The Effects of Prenatal Exposure to Methadone on Clinical and Neurobehavioural Outcomes of Infants Measured at Term

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List of Abbreviations

CADS	Canterbury Alcohol and Drug Services
CNS	Central Nervous System
F_0	Fundamental Frequency
GA	Gestational Age
ME	Methadone Exposed
MM	Methadone Maintenance
NAS	Neonatal Abstinence Syndrome
NBAS	Neonatal Behavioral Assessment Scale
NICU	Neonatal Intensive Care Unit
NNNS	NICU Network Neurobehavioural Scale

Abstract: This study examined the effects of prenatal exposure to methadone on clinical and neurobehavioural outcomes of infants between 40 and 42 weeks gestation. The aims of this study were: (a) to describe clinical and neurobehavioural outcomes of infants exposed to methadone during pregnancy, (b) to examine the effects of maternal methadone dose during pregnancy on infant clinical and neurobehavioural measures, and (c) to examine the extent to which associations between exposure to methadone during pregnancy and infant outcomes persisted after statistical control for a range of confounding variables. Two groups of study infants were recruited. These consisted of 51 consecutively recruited infants born to mothers maintained on methadone during their pregnancy and 42 randomly identified non-methadone exposed comparison infants. Prior to her child's birth, each pregnant woman completed a comprehensive maternal interview. At birth and during the infant's hospital stay a broad perinatal data-base was collected. At 42 weeks gestation infants underwent a neurobehavioural assessment including the NICU Network Neurobehavioural Scale (NNNS; Lester & Tronick, 2004) and infant cry analysis. Study results showed significant differences across several clinical and neurobehavioural measures. Infants exposed to methadone in utero were found to be significantly lighter ($p<.0001$), have smaller head circumferences ($p=.001$), and spend longer in hospital ($p<.0001$). Neurobehaviourally, they were significantly less well regulated ($p<.0001$), less attentive ($p=.004$), more easily aroused ($p=.001$), more excitable ($p<.0001$), and more hypertonic ($p=.001$). In addition, they exhibited less motor maturity ($p<.0001$), displayed more stress abstinence symptomatology ($p<.0001$), and required more support from the assessor in order to remain in an appropriate state ($p=.031$). Concurrent analysis of infant cry characteristics revealed no significant differences between the fundamental frequencies ($p=.764$) or the melody contours ($p=.453$) of the two groups. However, infants prenatally exposed to methadone did display higher levels of frequency perturbation in their cries, as evidenced by analysis of their jitter factor ($p=.012$) and percentage of directional jitter ($p=.015$). Analysis of the effects of maternal dose during pregnancy suggested that maternal dose levels above 60mg/day were general indicative of poorer infant outcomes than those below 60mg/day, with significant linear trends occurring across a number of measures. The extent to which associations between methadone exposure during pregnancy and infant outcomes reflected either a) the direct effects of methadone exposure and/or b) the effects of confounding factors correlated with maternal methadone use was examined using regression analysis. The results of this analysis for infant clinical outcomes showed confounding variables attenuated the effects of methadone exposure on infant birth length and, to some degree, infant head circumference. In contrast, associations between methadone exposure during pregnancy and most neurobehavioural outcomes remained significant, suggesting that maternal methadone use during pregnancy is an important, independent predictor of infant neurobehavioural functioning. These findings support the view that prenatal exposure to methadone has at least short term impacts on the infant's central nervous system (CNS) development. Important implications of possible vulnerabilities faced by these infants and their families are discussed.

The Effects of Prenatal Exposure to Methadone on Clinical and Neurobehavioural Outcomes of Infants Measured at Term

Introduction

1.1 Setting the Scene – An Overview of the Area of Opiate Abuse

1.1.1 The International Cost of Opiate Abuse

The social and economic costs of drug abuse and addiction are enormous. In the United States an estimated 10% of people suffer from alcohol or drug abuse or dependence, with over 7.5 million requiring treatment for a diagnosable drug problem and 18.6 million needing treatment for a serious alcohol problem. (U.S. Dept of Health & Human Services, 2003)

Similar statistics in New Zealand indicate that approximately 6% of people will meet clinical criteria for drug or alcohol abuse or dependence in their lifetime, with around 45,000 people receiving drug and alcohol assessment and treatment services each year (New Zealand Country Report, 2001).

Among the most used and abused of all illicit drugs are opiates. Naturally occurring opiates are derived from the resin of the opium poppy and have been used medicinally for centuries (Terry & Pellens, 1970). Opiates provide the user with an intense feeling of pleasure and wellbeing (commonly known as a "rush"), while feelings of pain, hunger, and sexual desire are diminished. However, opiates are highly addictive both psychologically and physically. The most commonly abused opiate derivative is the illicit drug heroin. Recent estimates suggest that as many as nine million people worldwide are dependent on heroin (United Nations Office for Drug Control and Crime Prevention as cited in Crandall, Crosby, & Carlson, 2004).

1.1.2 Treatment of Opiate Abuse

Both in New Zealand and internationally, the primary method of treatment for opiate addiction is methadone maintenance (Kandall, Doberczak, Jantunen, & Stein, 1999; Preston, 1999). Methadone (6-dimethylamino-4, 4-diphenyl-3-hepatone-hydrochloride) is a synthetically manufactured opioid agonist. Its properties are similar to those of other opiates in that it affects both the central and peripheral nervous systems. Methadone binds to the same peptides as other opiates, thereby reducing the cravings and withdrawal symptoms for those dependent on opiates. However, because it has a much longer half life, it does not provide the same peaks and troughs and is therefore considered a more "stable" drug (Preston, 1999). Hence, methadone substitution is used as a licit and controlled means of treating opiate dependence in order to help the user abstain from criminal activity and to facilitate a more productive and stable lifestyle.

Methadone maintenance treatment in New Zealand was first established in Christchurch during the early 1970s. In the late 1980s the evidence base for this maintenance modality, coupled with a greater awareness of the public cost of opiate addiction, led to an exponential increase in methadone maintenance enrolments, from 567 in 1990 to over 3,600 in 1999 (Preston, 1999). Waiting lists for methadone maintenance treatment programmes remain long.

1.1.3 Opiate Abuse and the Use of Methadone Maintenance Treatment During Pregnancy

Currently, women of childbearing age make up approximately half of all methadone maintenance enrolments in New Zealand (Fallowfield & Hood, 2004; Preston, 1999). In 1997, the National Institute of Health recommended methadone maintenance as the standard of care for pregnant women dependant on opiates (Berghella et al., 2003), despite pregnant women having been excluded from all randomized trails of methadone maintenance (Berghella et al., 2003). Growing enrolments, coupled with New Zealand's policy of considering pregnant women a priority group for methadone maintenance

treatment (Protocol for Methadone Maintenance Treatment in New Zealand, 2001), has resulted in increasing numbers of children being born to women maintained on methadone during their pregnancy.

Furthermore, the average methadone dose being prescribed to pregnant women also appears to be on the rise. Although earlier international guidelines recommended dose ranges of 20 -40 mg per day be used with pregnant women (Chasnoff, Hatcher, & Burns, 1982; Ostrea, Chavez, & Strauss, 1976; Rosen & Pippenger, 1976), more recently reported maternal doses are much higher (Berghella et al., 2003; Choo, Huestis, Schroeder, Shin, & Jones, 2004; McCarthy, Leamon, Parr, & Anania, 2005). To date there have been no empirically supported guidelines to aid clinicians in their decisions about the appropriate dosage and safe use of methadone maintenance during pregnancy.

Although research has generally demonstrated that methadone maintenance during pregnancy is associated with a significant number of benefits in comparison to illicit drug use, the teratogenic effects of methadone maintenance upon the developing foetus continue to be an issue of debate (Finnegan, 1991). In particular, given the apparent trends of increasing maternal dose, the possible implications of this is large. Both socially and economically there is a pressing need to empirically evaluate the newborn child and gain a better understanding of the effects of prenatal exposure to methadone.

1.2 Understanding the Effects of Methadone Exposure on the Developing Foetus

In order to better understand the implications of findings of methadone exposure at birth it is pertinent to first understand the possible mechanisms by which exposure in utero takes place. The following section provides a synopsis of how methadone affects the foetus in utero. It concludes with a section on the impact of methadone on the foetal brain and central nervous system (CNS).

In a simplified manner, the impact of methadone exposure on the developing foetus can be classified under pathways. Szeto (1995) described the impact of methadone exposure on the developing foetus as taking effect via two pathways: direct and indirect.

1.2.1 The Direct Pathway

The direct pathway primarily delineates the potential bio-pharmacological effects that occur via placental transfer of methadone from the mother to the opiate binding sites of the foetus. Given ethical boundaries, much of what is known about the pharmacology of the direct pathway comes from animal studies. It is known that methadone is transferred across the placenta, with this occurring as early as 14 to 16 weeks gestation (Blinick, Inturrisi, Jerez, & Wallach, 1975, cited in Rosen & Johnson, 1993). It is also evident that transfer occurs at increasing levels over the gestation period (Kandall et al., 1999). Research has shown that, at low doses, prenatal methadone exposure is associated with behavioural excitation of the foetus, tachycardia, EEG activation, and respiratory stimulation. In contrast, higher doses of methadone cause behavioural sedation, EEG slowing, and respiratory depression in the foetus (Szeto, 1995).

In recent years a small number of bio-medical studies have utilised human placental tissue to examine the circulation and metabolism of methadone in the foetus. Findings of one such study showed that although methadone is transferred very rapidly to the human foetus (with the majority of transfer occurring within the first hour), clearance of methadone occurs at a significantly higher rate from the foetus back to the mother (Nanovskaya et al., 2004).

1.2.2 The Indirect Pathway

The second pathway, known as the indirect pathway, encompasses all other methods by which maternal methadone might affect the developing foetus. This includes influences such as changes in maternal physiology and sociological factors related with maternal methadone use. This pathway exemplifies the need for a comprehensive understanding of the maternal pregnancy history and the need for a multidisciplinary approach to understanding the effects of methadone exposure on the developing foetus.

Indirect effects of methadone on the foetus via maternal physiology include depression in maternal respiration and reduction of uterine blood flow. These, in turn, alter the delivery of oxygen and substrates to the foetus which can result in foetal hypoxia or hypoglycaemia, both of which have been shown to affect foetal EEG and foetal breathing activity (Szeto, 1995)

Sociological factors implicated in the indirect pathway include factors related to environment and lifestyle choices. These include maternal health, prenatal care, and maternal nutritional intake, all of which need to be acknowledged as confounding the effects of methadone transferred via the direct pathway.

1.2.3 Impact on the Foetal Brain and Central Nervous System

The action of both pathways (direct and indirect) raises important concerns about the effects that prenatal exposure to methadone may have on the developing CNS in particular the foetal brain. A number of studies have examined this area more specifically. First, it has been shown that the brain is one of the primary organs used to store methadone during the gestation period (Kandall et al., 1999). Second, exposure to methadone has been shown to have disruptive effects on several neurotransmitter systems, including dopamine, norepinephrine, and serotonin within the brain (Malanga & Kosofsky, 1999; Robinson, Maher, Wallace, & Kunko, 1997). Third, both animal and human studies suggest that while methadone exposed infants may show relatively normal brain cytoarchitecture, they have been found to have smaller intracranial hemidiameter measurements and smaller lateral ventricle measurements, implying slower cortical cerebral growth (Nassogne, Gressens, Evrard, & Courtoy, 1998; Pasto et al., 1989). For example, Pasto et al. (1989) studied the sonographic characteristics of the cerebral ventricles, the transverse measurements of intracranial hemidiameter, right and left lateral ventricles, and temporal lobe and thalamic area measurements in 46 infants born to opiate dependent mothers and 31 controls. They found significantly different cerebral ventricle measures and smaller intracranial hemidiameter measures in the two groups. In a review of the mechanism of action of drugs of abuse, Malanga et al. (1999) argued that research has consistently shown that gestational opiate exposure results in a decrease in nucleic acid synthesis and protein production, both

of which are factors shown to impair brain growth. Robinson (2000) gave a thorough explanation as to how gestational methadone exposure may delay and disrupt cholinergic development, particularly in the striatum, which has been hypothesized to result in neuronal changes. Finally, Lester et al. (2003), examining the auditory brain stem response of one-month-old opiate exposed infants, found evidence for exposure affecting neural transmission. These findings suggest that there are likely to be both transient and persistent structural changes in the neurological development of infants prenatally exposed to methadone, raising important concerns about the neurodevelopmental effects that these changes may have on the child's future development.

1.3 Review of Previous Research on the Effects of Prenatal Methadone Exposure When Measured at Birth

The effects of methadone exposure on the CNS system of a developing human foetus discussed above can be understood as decreased neurodevelopmental integrity of the newborn infant, leaving the developing infant vulnerable to later difficulties. For instance, the findings of previous animal based research have suggested that prenatal exposure to methadone may result in both an increase in sensitivity to novel or reinforcing stimuli (Malanga & Kosofsky, 1999) and an impairment in directed motor co-ordination (Robinson, 2000). In order to have the least disruption to development it is important to identify and address potential vulnerabilities as early as possible. Therefore, it is essential to employ assessment techniques at birth to gain a better understanding of how these vulnerabilities may manifest in the newborn infant.

The following section reviews the findings of some of the more recent research on the effects of methadone exposure during pregnancy on the developing infant as measured at birth. A comprehensive review of earlier studies was undertaken by Householder, Hatcher, Burns, and Chasnoff (1982). For functionality and ease of understanding, this review will be divided into three sections:

1. Clinical outcomes associated with prenatal methadone exposure when measured at birth.

2. Neurobehavioural outcomes associated with prenatal methadone exposure when measured at birth, including discussion of neurobehavioural assessments and cry analysis.
3. Review of infant outcomes in relation to maternal methadone dose when measured at birth.

Appendix 1 provides a tabular overview of a number of studies relevant to the area.

1.3.1 Clinical Outcomes Associated with Prenatal Methadone Exposure When Measured at Birth

The simplest and possibly most rudimentary means of examining the effects of prenatal methadone exposure on the developing infant is via clinical measurements taken at the infant's birth. Clinical measurements include gestational age, weight, length, and head circumference. Almost all studies examining the effects of prenatal exposure to methadone at birth have provided at least two of these measurements. In many cases duration of hospital stay and infant APGAR scores are also considered as part of the infant's clinical outcome profile. APGAR scores are a popular quick and efficient measure of newborn health taken directly after birth (Apgar, 1953). The infant is assessed and scored across five measures: skin colour (**A**ppearance), heart rate (**P**ulse), reflex irritability (**G**rimace), muscle tone (**A**ctivity) and respiration (**R**espiration). Scores range between zero and ten. A repeatedly low score is indicative of an infant that requires immediate medical attention.

Previous research suggests that methadone exposed infants are at an increased risk for early delivery. A number of studies have calculated the mean delivery of methadone exposed infants as being around 38 weeks gestation (Jeremy & Hans, 1985; Kuschel, Austerberry, Cornwell, Couch, & Rowley, 2004; Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006; McCarthy et al., 2005; Rosen & Johnson, 1988; Sinha et al., 2001). Although this may not be considered premature (conventionally accepted as below 37 weeks), it is still lower than the typically accepted average of 40 weeks, and in conjunction with other clinical outcomes it is notable.

Several studies have found infants exposed to methadone in utero have lower birth weights; most typically citing mean weights around 2,700 gm (Berghella et al., 2003; Blinick, Jezez, & Walach, 1973; Hagopian et al., 1996; Kuschel et al., 2004; Lejeune et al., 2005; McCarthy et al., 2005; Rosen & Johnson, 1988; Sinha et al., 2001; Sharpe & Kuschel, 2003). Given the substantial lack of control groups and typically low sample sizes in these studies, significance levels relating to these lower birth weights are frequently not provided, but they are often notably lower than the New Zealand average of 3,410 gm (New Zealand Health Information Service, 2003).

Surprisingly few of the studies reviewed have provided information on infant birth length, and those that have recorded length have generated a mixture of outcomes. Chasnoff, Burns, Burns, and Schnoll (1986) found a significant difference between the birth lengths of infants prenatally exposed to methadone (n = 51) in comparison to non-exposed controls (n = 27). However, Lester et al. (2002) reported no significant differences in birth length between 119 opiate exposed infants and a large sample of infants not exposed to opiates (n = 1,273). Sharpe and Kuschel (2003) found no significant difference between the birth lengths of 24 infants born to women on methadone maintenance treatment and birth lengths of children of 19 women prescribed methadone for the management of maternal pain, but did not compare either group to a non-exposed comparison group.

Several previous studies conducted with infants exposed to methadone have noted that they have smaller head circumferences at birth (Bada et al., 2002; McCarthy et al., 2005; Rosen & Johnson, 1988; Sharpe & Kuschel, 2003). This is an important finding because head circumference has been directly correlated with IQ (Rushton & Ankney, 1996).

Taken together, the clinical findings listed above may provide an indication of early vulnerability in these infants. Several studies of premature and/or low birth weight infants acknowledge a strong correlation between decreasing gestational age and birth weight and increasing rates of disability, including social, behavioural and learning problems (Davis, 2003; Hack & Fanaroff, 2000; Taylor, Klien, & Hack, 2000), with one article stating that, “the relation between birth weight and IQ is usually linear in low birth weight groups – that is, the smaller the newborn the lower the IQ” (Wolke, 1998, p. 567).

Duration of hospital stays of these infants have been measured in a variety of ways. With some authors providing information on time in Neonatal Intensive Care Unit (Hagopian et al., 1996; Lejeune et al., 2006; Sinha et al., 2001) while others provide total time in hospital (Blinick & Jerez, 1973; Choo et al., 2004). Those studies that have provided information on the duration of infant hospital stay have cited means ranging from four days in NICU (Hagopian et al., 1996) to 23 days in NICU (Lejeune et al., 2006). For those that have provided information on total duration of stay, days in hospital have ranged as high as 80 days (Choo et al., 2004). One study that specifically examined maternal drug use and the length of neonatal hospital stay reported that duration of stay was longest for infants exposed to methadone and other drugs (Johnson, Greenough, & Gerada, 2003). However, it should be remembered that caution needs to be taken when interpreting mean duration of infant hospital stay due to the variation in management and regulations of different hospitals across countries and regions.

Finally, the only reported difference on APGAR scores at term was located in an older study in which ten percent of methadone exposed infants had depressed APGAR scores at birth (Blinick, Jezez, & Walach, 1973).

1.3.2 Neurobehavioural Outcomes Associated with Prenatal Methadone Exposure When Measured at Birth

1.3.2.1 Neonatal Neurobehavioual Assessments Outcomes

A more sophisticated means of gauging the effects of prenatal methadone exposure at birth is via neurobehavioural assessments. These assessments determine the medical status of an infant via behavioural manifestation of the structural changes in CNS hypothesized to occur during foetal development (Mayes & Ward, 2003). In more simple terms, these assessments utilise the bi-directional nature of behaviour and neurological functioning to assess the infant on behavioural signs of neurological impairment. This provides a functional understanding of the nature of neurological impairments that can then be used to identify at risk infants and develop strategies to minimise areas of vulnerability.

The use of neonatal neurobehavioural assessments began in the mid 1900s, with early assessments utilising muscle tone and early reflexes to gauge an understanding of the infant's neurological status. From the later 1950s to the 1970s assessments advanced through the addition of more behavioural and attention-interactional components. One of the most well known newborn neurobehavioural assessments, the Neonatal Behavioral Assessment Scale (NBAS), developed by T. Berry Bazelton (1973), was developed around this time. More recently, neurobehavioural measures have been designed to assess specific populations. In neonates this includes areas such as prematurity (Premie-Neuro by Daily & Ellison, 2005) or neonatal drug exposure (NICU Network Neurobehavioural Scale, NNNS by Lester & Tronick, 2004).

Typically, neurobehavioural assessments of infants exposed to drugs in utero have considered the behavioural symptomatology of neonatal abstinence syndrome (NAS). Studies suggests that as many as 48 to 95% of infants exposed to methadone in utero will show signs of neonatal abstinence (Preston, 1999; Sinha et al., 2001; Sarkar & Donn, 2006). Evidence suggests that the incidence and severity of neonatal abstinence from methadone may be greater than in infants exposed to heroin and other opiates (Johnson et al., 2003). The combination of previous bio-medical and neurobehavioural research posits that although methadone may leave the blood stream within a few days of birth (Rosen & Pippenger, 1976, cited in Jeremy & Hans, 1985) it is excreted much more slowly from the body tissue to which it binds (Jaffe & Martin, 1980, cited in Jeremy & Hans, 1985). This delay results in the later onset of NAS, typically beginning between the second and fourth day (Sinha et al., 2001) with previous researchers finding that drug-free urine usually occurs around 7 to 21 days (Rosen & Johnson, 1993). As stated by Jeremy and Hans (1985), "while we are not able to answer questions about the biochemical status of withdrawal in these infants, their behavioural recovery is likely to be a good reflection of their status" (p. 325).

Chasnoff, Schnoll, Burns, and Burns (1984) and Jeremy and Hans (1985) both utilised the NBAS to examine the neurobehavioural differences between newborn infants exposed to methadone during pregnancy and non-exposed controls. Relative to controls, infants

exposed to methadone were jerkier, tenser, more active, more irritable, and had difficulty with state control.

Other studies utilising neurobehavioural measures have found evidence that infants exposed to methadone in utero have higher levels of irritability, lower levels of consolability, poorer state regulation, increased levels of overall activity coupled with decreased motor maturity, and reduced interacting responsiveness than comparison infants (Berghella et al., 2003; Blinick, Jezez, & Walach, 1973; Hagopian et al., 1996; Kuschel et al., 2004; Lejeune et al., 2006; McCarthy et al., 2005; Rosen & Johnson, 1988). Others have noted infant tremors, abnormal and ineffectual sucking, irregular postures, and sleep disturbances in exposed infants (Kaltenbach et al., 1987; Moore, Negrusz, & Lewis, 1998; Rosen & Johnson, 1993).

Although many of these studies have demonstrated a consistent neurobehavioural profile, the majority have a number of methodological shortcomings. Primarily, the majority have used older neurobehavioural measures not specifically designed for use with infants exposed to maternal drug use during pregnancy and have failed to consider the influence of confounding variables. A more detailed discussion of the limitations of previous research is included in a later section.

1.3.2.2 Acoustic Cry Analysis Findings

Another form of neurobehavioural assessment is acoustical cry analysis. Since the early 1960s, acoustical analysis of infant crying has been used as an inferential gage of a child's neurodevelopmental integrity. Because cry represents a combination of respiratory, laryngeal, and vocal tract functions, any unusual or deviant cry patterns are likely to be a reflection of poor organisation in either parasympathetic or sympathetic strands of the nervous system. In the early 1980s, Golub and Corwin (1985) developed a bio-behavioural model (known as the physioacoustic model) of infant crying that includes various acoustic parameters of crying and how they relate to the physiology and CNS of the infant. Appendix 2 provides the visual conceptualisation of the model offered by Golub and Corwin. The most common acoustic features examined in infant crying are fundamental

frequency (F_0), cry duration, and the first and second formant frequencies (F1 and F2). Measurement of F_0 is used to infer laryngeal behaviour, namely vocal fold vibration (i.e., pitch). Measurement of cry duration is used to infer respiratory effort, with respiratory capacity correlated with the overall length of infant crying. Measurement of F1 and F2 frequencies is used to infer vocal tract articulation, namely vocal resonance.

Although acoustic cry studies have been performed for some time, there are still surprisingly few studies of newborn cries, and the sample sizes used are typically quite low (Michelsson, Eklund, Leppanen, & Lyytinen, 2002). However, studies have successfully used acoustic cry analysis to detect subclinical effects in a variety of medical conditions and potential nervous system insults. A comprehensive listing of these, as summarized in Cacace, Robb, Saxman, Risemberg, and Koltai (1995), included "infants with chromosomal abnormalities, metabolic disorders, asphyxia, meningitis, cleft palate, laryngitis, unilateral vocal chord paralysis, sudden infant death syndrome, as well as infants that were premature, malnourished and whose mothers were addicted to heroin or who had used marijuana, cocaine or alcohol excessively" (p. 214). Additionally, a more recent review of the cry literature also included infants with the medical conditions of Krabbe's disease, hypothyroidism, hydrocephalus, Down syndrome, and cri-du-chat as well as infants prenatally exposed to methamphetamines, tobacco, and lead (LaGasse, Neal, & Lester, 2005).

Laryngeal behaviour appears to be influenced by abnormalities of CNS functioning. Such being the case, the acoustic parameter of F_0 is often revealing of differences between healthy term babies and those of at-risk babies (Michelsson, Eklund, Leppanen, & Lyytinen, 2002). For example, Michelsson and Michelsson (1999) performed an acoustic analysis of pain cries on low birth weight and typical birth weight infants at 10 days of age and found that low birth weight infants were more likely to have a higher F_0, display more rapid changes in F_0 (gliding), and have more biphonation (evidence of two simultaneous F_0 patterns). Similarly, Zeskind, Platzman, Coles, and Schuetze (1996) examined the effects of prenatal alcohol exposure and found that at 14 days of age, exposed infants had reliably higher peak F_0. The perceptual aspects of F_0 (i.e., voice pitch) have also provided confirmation of cry abnormality. Studies reviewing the perceptions of high pitched cries

from vulnerable or ill infants have found that they are generally rated as more aversive and sick sounding (LaGasse et al., 2005; Ziefman, 2004)

Another related, albeit less frequently used, cry measure of F_0 is that of frequency perturbation. More commonly referred to as jitter or vibrato, frequency perturbation reflects the microfluctuations present in cycle-to-cycle differences in the F_0 over time. In simple terms, jitter can be interpreted as an indicator of vocal stability. Given the premise that perfect control of the phonatory system would reflect no jitter, increased levels of jitter can be viewed as reduced control of the phonatory system (Baken, 1987). This is confirmed by findings that jitter tends to increase in vocal pathology (Orlikoff & Baken, 1993). As a reflection of this, an earlier study by Graul, Hock, and Rothenger (1990) postulated that the jitter index of a pain cry yielded the best discriminatory parameter for the characterization of "normal" versus "disturbed" crying behaviour.

Within the cry literature to date there has been a small amount of research into the cry characteristics of infants exposed to maternal opiate use during pregnancy (Blinick et al., 1971 and Corwin et al. 1987 cited in LaGasse et al., 2005; Lester et al., 2002). Results from these studies parallel results obtained from infants known to demonstrate central nervous system insults. In general, the cries are characterised by a high F_0 and short cry duration in comparison to controls. To date there appears to be only one study examining the cry characteristics of infants exposed to methadone in utero, that done by Huntington, Hans, and Zeskind, 1990. This study examined the average F_0, F_0 variability, peak F_0, and duration of the first expiratory cry in eight infants prenatally exposed to methadone in comparison with 12 control infants matched for socio-economic status at two to three days old. As opposed to the findings of those that examined other opiate exposure, the results of this study found no difference across the measures of F_0, and found that only the duration of the first cry differentiated the two groups. However, across both groups they found that cry characteristics did relate to later measures of developmental functioning.

The review of literature in the area of infant cry provides a strong rationale as to why there is further need to investigate the cry characteristics of infants exposed to methadone during pregnancy. First, given the growing rates of prenatal methadone exposure and the uses of

infant cry analysis as a neurobehavioural gage of infant integrity it is surprising there has been only one study in this area. Such being the case, a clear profile of the cry behaviour in methadone exposed infants has yet to be established. Second, the conflict between the findings of Huntington et al. (1990) and those from studies examining other opiate exposure (Blinick et al, 1971 and Corwin et al, 1987 cited in LaGasse et al., 2005; Lester et al., 2002) indicates the need for further exploration utilising a more fine-grained measure of analysis, such as the use of F_0 perturbation.

1.3.3 Review of Infant Outcomes in Relation to Maternal Methadone Dose When Measured at Birth

Another means of examining the effects of exposure to maternal methadone during pregnancy is to consider the impact of maternal methadone dose. However, a dose response relationship between maternal methadone dose and infant outcome has been difficult to establish (Finnegan, 1991; Kaltenbach, 1994). Some researchers have found evidence for a relationship (Dashe, Sheffield, Olscher, Todd, Jackson, & Wendel, 2002; Malpas, Darlow, Lennox, & Horwood, 1995; Sharpe & Kuschel, 2003; Sinha et al., 2001), while others have not (Brown, Bakeman, Coles, Sexson, & Demi, 1998; Jeremy & Hans, 1985; Kuschel, et al., 2004; McCarthy et al., 2005).

A study by Dashe et al. (2002) is typical of those finding a dose response relationship. They undertook a retrospective study of 70 women between the years of 1990 and 2001. They showed that methadone dose (based on maximum daily intake over the last week of pregnancy) correlated with the duration of neonatal hospitalisation, the neonatal abstinence score, and treatment for withdrawal (median dose 20 mg, range 0-150 mg). Both the maternal dose and the extent of infant treatment increased over the time period, with those on a higher methadone dose more likely to have been using illicit heroin as well. Similarly, a local Christchurch study by Malpas et al. (1995), again using a retrospective design, covering the period from 1987 to 1991, showed strong correlation between maternal methadone dose and both length of hospital stay and duration of neonatal treatment across the 40 mother-infant dyads studied.

In contrast, another retrospective (1996-1999) study of 100 mother/infant pairs around the same period found no evidence for a dose response relationship. Berghella et al. (2003) examined both average methadone dose during last 12 weeks of pregnancy and last methadone dose before delivery with a high/low cut-off of 80 mg/day. Highest neonatal abstinence syndrome scores and length of neonatal abstinence syndrome were similar for both groups across both methods of comparison. These authors suggested that a confounding variable, benzodiazepine use, may have been responsible for greater symptomatology of neonatal withdrawal.

Despite the lack of overwhelming evidence for either side of the dose argument, trends in the administration of maternal methadone doses appear to be increasing over time (Wouldes & Woodward, submitted). This is possibly a reflection of current policy coupled with the natural increase in metabolism of methadone during pregnancy. Current policy in regards to both New Zealand and the United States suggests increasing methadone doses in pregnant women in accordance with the woman remaining symptom free with either arbitrary or no limits (Berghella et al., 2003; McCarthy et al, 2005). Despite the fact that optimum serum trough levels (between 150-600 ng/mL) have been established for non-pregnant users of methadone maintenance treatment, there appears little or no attempt to adhere to these levels (Mccarthy et al., 2005). Likewise, despite the fact early international guidelines (although never empirically validated) recommended methadone dose levels of between 20-40 mg/day (Chasnoff et al., 1982) the reality is that these are often exceeded today and for example, the mean dose levels currently reported in New Zealand literature are closer to 65 mg/day (Wouldes, 2004).

1.4 Methodological Issues and Limitations of Previous Research

The following section outlines in more detail the methodological issues and limitations of the past research. These shortcomings provide further rationale in regards to the need for the current study.

1.4.1 Age of Previous Studies

A large number of the studies which initially examined the effects of prenatal exposure to methadone were conducted in the 1970s. Now, more than a quarter of a century later, there have been several changes and advances in both medical knowledge and neonatal intensive care procedures. This is likely to have influenced findings as neonatal mortality rates have been significantly reduced (Preston, 1999) and more refined measurements for testing and data collection are now available.

Furthermore, as already stated, there has been a general rise in maternal dose over the past three decades. One recent study by McCarthy et al. (2005) used 100 mg/day as the cut-off between high and low maternal doses. When compared with the earlier studies such as Chasnoff et al. (1984) or Jeremy and Hans (1985) who quote maternal ranges between 3-40 mg/day this trend is quite apparent. Average maternal dose in New Zealand also appears to be above the early international recommendations. For example Wouldes (2004) reported the mean dose prescribed in Auckland drug treatment centres at 64.8 mg/day (range: 4-125 mg).

1.4.2 Lack of Control Groups

A fairly comprehensive review of the earlier studies by Householder et al. (1982) lamented a general lack of control groups in this area of research and stated that in "the majority of the studies that do report control groups, populations are frequently poorly defined or are not well balanced in terms of important demographic variables", (p. 463) citing differences in racial breakdown as a prime example. Despite this, newer studies have continued to lack control groups (Choo et al., 2004; Kuschel et al., 2004; McCarthy et al., 2005) or only provided selective comparison groups making findings harder to generalise (Fajemirokun-Odudeyi et al, 2006; Lejeune et al., 2006; Sharpe & Kuschel, 2003).

1.4.3 Procedural Inadequacies

Several criticisms can be made of the procedural methods used in many of the studies in this area. In particular, a substantial majority of studies in this area are approached as a retrospective study of hospital or clinic records (Berghella et al., 2003; Fajemirokun-

Odudeyi et al, 2006; McCarthy et al., 2005; Sharpe & Kuschel, 2003). Although useful, this type of research has been criticised for using what are known as "post hoc" analyses. That is, the hypotheses to be tested and interpretations of causality are made after the data has already been collected. This can lead to an increased probability that results will be statistically significant (a Type I error). In order to examine a true association, hypotheses should be established first. Hypotheses should then be tested via manipulation of the independent variable on a target population. Finally, this target population should be evaluated against a randomly selected control population and differences between the two measured.

A further criticism is the use of routine and changing hospital staff, for example nurses, in order to gather data. This is the case for almost all retrospective studies but also a number of prospective studies. (Choo et al., 2004; Hagopian et al., 1996; Sinha et al., 2001). This has several methodological drawbacks. First, subjective differences from utilising multiple assessors may have increased measurement inconsistency and error. Second, training requirements and inter-rater reliability of different raters are generally not documented. Third, the accuracy of measures may not have been as precise as are required in research. For instance, when measuring infants' head circumferences a matter of millimetres may make no functional difference for hospital staff but may reflect significant differences in research populations.

1.4.4 Measurement Inadequacies and the Role of Confounding Variables

Inadequacies can also be found in regards to the measurement tools used in this area of research. A number of earlier studies examining the neurobehavioural implications of drug exposure in utero used assessment measures that were not designed specifically for use with substance-exposed infants, such as the Brazelton Neonatal Behavior Assessment Scales (NBAS) (Jeremy & Hans, 1985; Rosen & Johnson, 1988). It is therefore likely that data gathered may not be as comprehensive or useful as is currently possible. Other frequently used assessment scales, such as Finnegan's Neonatal Abstinence Scoring System (Finnegan, Kron, Connaughton & Emich, 1975), offer a subjectively interpretable checklist of items, therefore limiting the value of the information. In addition, the use of

the Finnegan's Neonatal Abstinence Scoring System has been criticised in regards to its complexity and questioned as to the appropriateness of its use in busy clinical settings (Sarkar & Donn, 2006). Worse still, a few studies have provided little or no information at all on what measure(s) were used (Fajemirokun-Odudeyi et al., 2006; Hagopian et al., 1996; Sinha et al., 2001). This can be particularly complicated given the lack of consistency and diversity of quality of tools used across this area of research.

Similarly, in the area of cry analysis, there have been improvements in the technology related to signal processing that should be noted. In the past sound spectrography involved hand measures of spectrograms. Therefore, there has been a shift in the literature from the use of sound spectrography to newer computer aided digitisation of infant cries (often referred to as fast Fourier Transform or FFT). However, FFT has significantly reduced the finer detail of information gleaned from infant cries. It has been acknowledged by others (Berge et al., 1984 cited in Hopkins, 2000) that these computerised systems are not good at adequately identifying the components of a sound signal, for example, differentiating adult talking from an infant cry and FFT typically ignores more fine grained changes in the F_0 over time. Although computerised systems may provide a fast and efficient means of analysing basic components of infant cry (for example, maximum and minimum F_0) some of the most sensitive measures such as F_0 frequency perturbation (jitter) are lost. Given the advances in computerisation of sound spectrography use of this method is likely to provide more accurate results of infant cry.

Two additional areas of measurement inadequacy in regards to cry research should also be noted. These are: 1.) sampling differences across infant crying and 2.) differences in the method of eliciting cries and types of cry elicited. First, previous researchers have sampled infant cry in a variety of different ways. While some have focused on the beginning of the infant cry and the first few utterance (Huntington et al., 1990; Lester et al., 2002) others have argued that information across the entire cry bout is pertinent (Gobermann & Robb, 1999). Similarly, as explained by Hopkins (2000) while some researchers have included all sounds including fuss and whimpers as cry others have more narrow definitions. Second, infant cries have been elicited in a variety of ways and to date there remains no standardised procedure. As discussed in Cacace et al., (1995) techniques have ranged from

rubber bands to the infants heal, to vaccinations, to removal of electrodes used to monitor the infant's heart and respiration. Alternative methods have also included physical manipulation of the infant or the use of newborn reflexes. The aim of all these methods is to fully activate the infant's CNS yet little detail is often given as to why a procedure was chosen. Relatedly, the use of noxious stimuli to elicit infant cries has been criticised in regards to the detrimental loss of information of spontaneous, more naturally occurring cries (Green, Irwin & Gustafson, 2000).

Finally, an important measurement shortcoming that has been repeatedly raised in regards to understanding the effects of prenatal methadone exposure is the lack of consideration of confounding variables (Householder et al., 1982; Jacobson & Jacobson, 2005; Kaltenbach, 1994). This is a well acknowledged and difficult aspect in regards to any research examining the effects of drug exposure in utero. The most significant of these confounding variables is that of poly drug use and abuse. Indeed, single drug use is considered relatively rare with a large proportion of women acknowledging multiple drug use during pregnancy (Lester et al., 2001 cited in Coles and Black, 2006). This is difficult to take into account on several levels. First, given the illegality of most drug use women are frequently reluctant or unwilling to disclose information about personal use because of both legal and social consequences (Schuetze & Eiden, 2006). Second, alternative methods of verifying poly drug use, such as meconium or hair analysis, may be costly or difficult to arrange and are therefore often under utilised. Although most studies acknowledge the high probability of poly drug use in these pregnant women, few have run analyses that factor out the effects of poly drug use thereby making the influence of methadone itself difficult to extract from the related, often well established, risk factors (for example cigarette use or alcohol use during pregnancy). Studies that have considered confounding variables often suggest these have a strong influence on newborn outcomes. For example, Choo et al., (2004) suggested that maternal tobacco use during pregnancy may influence the timing and severity of NAS exhibited by infants prenatally exposed to methadone.

Other confounding variables that are often less considered but have also been raised as important variables to consider are sociological variables (Kaltenbach, 1994). These include, but are not limited to, maternal age, maternal health, ethnicity and socio-economic

status. Although a skewedness in many of these variables may be a realistic representation and considered part and parcel of a drug abusing population a number of these factors are also proven risk factors that have been shown to influence foetal development and should therefore be considered or at least presented as maternal background data alongside the pregnant woman's drug use. Indeed, Cole and Black (2006) suggest that "the interaction between the effects of the teratogen and the effects of the environment is probably the most interesting scientific question in the field at this time" (p. 3).

1.5 Synopsis of Previous Findings and their Limitations

The majority of studies already conducted in the area of infant exposure to methadone in utero have utilised both clinical and neurobehavioural measures. Clinical measures commonly include gestational age, birth weight, head circumference, APGAR scores and duration of hospital stay. Findings have shown that infants exposed to methadone in utero are often born earlier, are lighter, have smaller head circumferences and longer stays in hospital.

A variety of neurobehavioural measures have been used assess infants outcome. Findings have shown that infants exposed to methadone often show signs of withdrawal, may be easily upset, exhibit poorer but often more hypertonic muscle control and display difficulty in ability to self-regulate. However, the complexity, design and sophistication of the measures vary considerably. Additionally, one study used infant cry analysis as a means of establishing the neurodevelopmental integrity of these infants. In contrast to other neurobehavioural measures this method found very few indications of difference between infants prenatally exposed to methadone and controls.

However, previous research has several methodological limitations. Research is generally outdated, either having been conducted several decades ago, or utilising dated or unrefined measures. Few studies have utilised appropriate control groups, many have procedural inadequacies and the majority have not adequately considered the role of confounding variables.

1.6 The Current Study – Research Questions and Hypotheses

The current study examines the effects of prenatal exposure to methadone on the clinical and neurobehavioural outcomes of infants at term. It addresses a number of the drawbacks of previous studies by utilising a prospective, between groups approach in combination with a number of comprehensive and up-to-date measures. Furthermore, it addresses the current debate of whether or not maternal methadone dose influences the outcome these infants and examines the much neglected issue of confounding variables.

This final section explicitly outlines the aims and hypotheses of the current research.

Specific Aim One

To compare the effects of prenatal exposure to methadone on the clinical and neurobehavioural outcomes of infants at term. Infants born to mothers maintained on methadone during their pregnancy are compared with a sample of randomly identified non-exposed infants. Clinical outcomes include birth weight (gms), birth length (cm), head circumference (cm), infant APGAR scores and duration of hospital stays. Neurobehavioural outcomes include the NNNS assessment and infant cry acoustics.

Hypothesis One

At term, infants born to methadone maintained women will have lower birth weights, smaller head circumferences and longer hospital stays than the comparison infants.

Hypothesis Two

At term, infants born to methadone maintained women will perform less well on a standardised neurobehavioural assessment compared to the randomly identified, non-exposed infants. Specifically, infants exposed to methadone in utero will display poorer quality of movement, poorer regulation capacities and decreased attentional abilities, while demonstrating higher levels of non-optimal reflexes, muscle tone and stress/abstinence symptomatology in comparison to the non-methadone exposed infants.

Hypothesis Three

At term, the cry acoustics of infants born to methadone maintained women will have a higher and more variable F_0, shorter cry utterances and abnormal cry configurations when compared to the cries of non-methadone exposed infants.

Specific Aim Two

To examine whether higher maternal doses of methadone during pregnancy are associated with poorer clinical and neurobehavioural (NNNS) outcomes of these infants at term.

Hypothesis Four

Higher maternal methadone dose will correlate with lower infant birth weight, reduced infant head circumference and increased symptomatology of neonatal abstinence.

Specific Aim Three

To examine the role of confounding variables in relation to the findings reported in regards to the previous aims. Using statistical techniques, models outlining the role of confounding variables and their relationship to the impact of prenatal methadone exposure are constructed and interpreted.

Hypothesis Five

Confounding variables will reduce but not eliminate the effects of methadone exposure on the developing foetus. Certain confounding variables, such as cigarette use during pregnancy, will have an important role in accounting for any variance found between the infant's exposed to methadone in utero and the comparison non-exposed infants.

Methodology

2.1 Ethical Approval of the Current Study

The current study was undertaken as part of a larger multi-site study run by the Child Development Research Group at Canterbury University. Ethical approval for the current study was obtained by the senior investigator, Dr. Lianne Woodward under an umbrella application for the complete term assessment for the larger study (Woodward, Inder, McKie, Wouldes & Kuschel, 2002). Ethical approval was obtained from the Canterbury Ethics Committee.

2.2 Participants and Recruitment

The methodology of the current study used a prospective, between groups approach.
The following two groups were included in this study.

2.2.1 Group 1 – Methadone Maintenance Group

Fifty pregnant women consecutively enrolled in the Christchurch Methadone Maintenance Programme were recruited via the Methadone in Pregnancy Clinic provided by the Women's Health Division of the Canterbury District Health Board (CDHB). These women were referred via the Community Alcohol and Drug Service (CADS) Methadone Maintenance Programme between November 2002 and December 2005. Recruitment of this group was conducted by a research nurse from Christchurch Women's Hospital as part of the larger study. The research nurse attended the methadone clinics and the antenatal classes that all methadone maintained women attended as part of their treatment. At these meetings she offered information on the study, answered women's questions and obtained consent from those women who agreed to participate. On a number of occasions the research nurse was also accompanied by the research group's Maori cultural health advisor to ensure that any cultural needs were being met and to ameliorate any culturally-based

biases that may have been occurring at the recruitment stage. All women involved with the CADS Methadone Maintenance Programme give birth at Christchurch Women's Hospital. This enabled the research nurse to be available for these women and also to inform members of the research group when a recruited infant was born.

Exclusion criteria for this group included infants born with serious congenital abnormalities, still births and premature deliveries of less than 33 weeks gestation. For pragmatic reasons, pregnant women who were unable to speak or understand English sufficiently to give informed consent and those outside the Canterbury region were also excluded from the study. In addition, three pregnant women on the methadone maintenance programme who did not regularly attend the methadone maintenance programme and therefore whose methadone dose records were incomplete were excluded.

Table 1 displays the recruitment statistics for the methadone exposed group. A total of 76 pregnant women were approached of which, 50 agreed to participate. This equates to a recruitment rate of 66%. However, of the 26 that did not agree to participate, over half were not recruited due to ineligibility criteria for instance living outside of the recruitment area, lack of consistent attendance at the methadone clinic or termination of pregnancy. The remaining ten ineligible cases were refusals to consent, either by the pregnant women herself (n = 7) or refusal by her partner (n = 3). After factoring out ineligible cases (n = 16), the recruitment rate for this group can be considered 82%.

Table 1

Recruitment Statistics of the Women Enrolled in Methadone Maintenance Treatment

Recruitment type	Number of participants	% of total contacted
Contacted	76	100
Recruited and Consented	50	66
Not recruited	26	34

Ineligibility Criteria	Number of participants	% of total not recruited
Participant refused	7	27
Partner of participant refused	3	12

Foetus ineligible*	8	31
Other ineligibility**	8	31

*congenital abnormalities, still birth, miscarriage, termination, born less than 30 weeks gestation

**out of catchment area, irregular attendance of methadone programme, not able to understand English sufficiently

2.2.2 Group 2 – Non-Methadone Exposed Control Group

Over the same period, 42 pregnant women used for control comparisons were recruited at random from the Christchurch Women's Hospital delivery database. Randomisation was used to identify control participants in order to provide a representative sample of non-methadone exposed comparison infants. A randomized method of recruitment was chosen because previous experience attempting to match for factors such as cigarette smoking have proved to be extremely difficult to achieve due to low rates of disclosure (Wouldes, 2004). Furthermore, by using random recruitment it was anticipated that the disclosed rates of cigarette smoking and other drug use would more accurately represent national/regional rates, thus allowing these factors to be included as covariates in the multivariate analyses of the relationship between methadone exposure and infant outcome.

The recruitment of the control mother-infant dyads was conducted by the author of the study with aid from the research co-ordinator of the larger study. A database including names, addresses and expected dates of delivery of all women listed to give birth at Christchurch Women's Hospital was obtained via the hospital affiliated research nurse. A random number generator (www.randomizer.org) was then used to decide which women to contact. Women were selected approximately two months before delivery to allow for larger numbers on the database while enabling enough time to complete study enrolment prior to delivery. The number selected each month varied depending on the number of methadone infants due. Once selected, names and hospital numbers were sent back to the research nurse in order to cross-check eligibility. Information letters were then mailed out to all randomly selected women along with a contact number to call if interested. Follow up calls were made approximately a week later to all women who had called over the

previous week. For those women who did not return the invitation to participate, a follow up telephone call or visit in person was made to enquire if they were interested. On several occasions where no phone number was available the author door knocked at the addresses provided to try to enlist those randomly selected. Thus, several endeavours were undertaken to ensure that those randomly selected were provided with a number of opportunities to participate. At follow-up phone calls or home visits, further information was provided regarding the study and pertinent questions were answered. Consent from this group of women was obtained upon initial physical contact prior to being interviewed.

As with the women in the methadone maintenance group, exclusion criteria for those in the control group included, infants born with serious congenital abnormalities, still births and premature deliveries of less than 33 weeks gestation. Pregnant women who were unable to speak or understand English sufficiently to give informed consent and those outside the Canterbury region were also excluded from the study.

Recruitment statistics relating to the control women are presented in Table 2. Of the 92 letters posted out 42 women were successfully recruited. This equates to a recruitment rate of 46%. After factoring out those women that were ineligible for instance, due to congenital birth defects of the foetus or lack of sufficient understanding of English to provide informed consent, the recruitment percentage increased to 51%. Of those in the control group the majority of women not recruited were due to participant refusals (n = 25) as opposed to partner refusals. However, a sizeable number (n = 12) were also not recruited due to the fact they could not be located from the contact information provided despite multiple endeavours from the research recruiters.

Table 2

Recruitment Statistics of the Non-Methadone Exposed Control Group

Recruitment type	Number of participants	% of total contacted
Contacted	92	100
Recruited and Consented	42	46
Not recruited	50	54

Ineligibility Criteria	Number of participants	% of total not recruited
Participant refused	25	50
Partner of participant refused	3	6
Un-locatable*	12	24
Other ineligibility**	10	20

*addresses of women were incorrect and no forwarding address or alternative address was available

**congenital abnormalities in foetus, pulled out after consenting, not able to understand English sufficiently, moved out of area

2.2.3 Analyses of Maternal Background Characteristics

Table 3 describes the maternal and family background characteristics of women enrolled in the methadone maintenance programme and women in the non-methadone exposed group. A range of characteristics across several domains were examined including, maternal age, marital status, ethnicity, schooling and living circumstances. Each comparison was tested for significance using the chi squared test of independence for dichotomous measures (presented in percentages) or independent samples t-tests for continually distributed variables (presented with means and standard deviations). The information provided on this table was based on questions included in the maternal interviews which were completed by each pregnant woman prior to their infant's birth and was supplemented with data from hospital records.

The results in Table 3 show significant differences between the two groups occurred across the areas of relationships, schooling, finances and accommodation. In regards to relationships, women in the methadone maintenance group were significantly more likely to be un-married ($p < .0001$) and have been in the current relationship for approximately half as long as the comparison group (43 versus 80 months in a relationship). They were also significantly more likely to have received no formal schooling ($p < .0001$), be unemployed ($p < .0001$) and to be receiving a social welfare benefit ($p < .0001$). The most frequently endorsed type of accommodation for women in the methadone maintenance

group was "living in rented accommodation" (55%) while the equivalent for the comparison women was "living in own home" (48%).

No significant between group differences were found on measures of maternal age and ethnicity. As shown, across both groups the ethnicity primarily identified with was New Zealand European. This was the case for 66% of the methadone maintenance group and 60% of the control comparison group. When combined with those that endorsed "Other European" the totals for the two groups are 72% and 67% respectively. The second most commonly identified ethnicity, also across both groups, was New Zealand Maori. Eighteen percent of the methadone maintenance group and 14% of the control group identified themselves as NZ Maori. These figures are relatively consistent with details gathered from New Zealand Census information. The 2001 New Zealand Census reported that Europeans constituted 79% of the ethnic share of New Zealand population while Maori constituted 15% (Statistics New Zealand, 2005).

Table 3

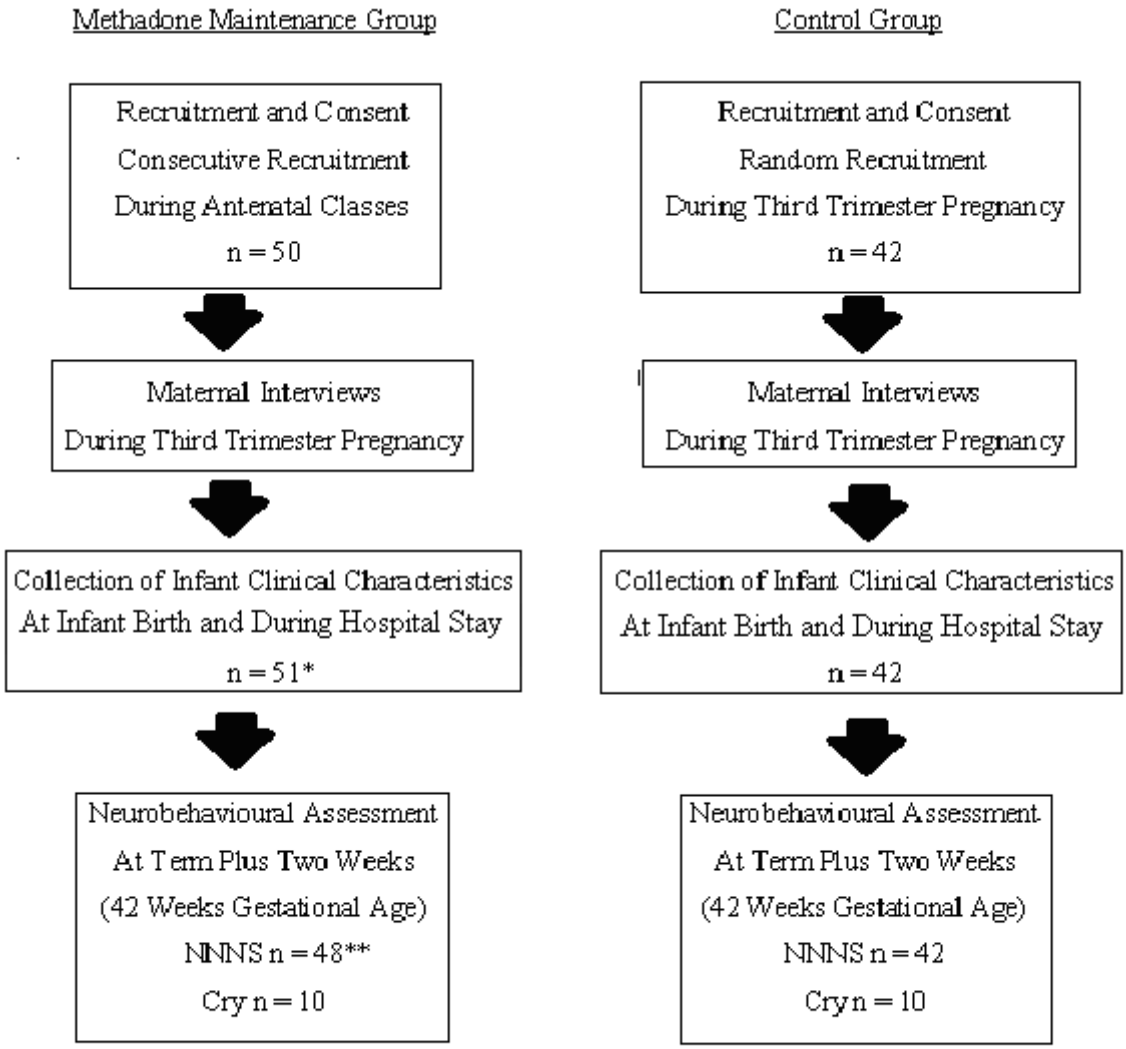
Comparisons of Maternal Background Characteristics

Measure	MM (n = 50)	Control (n = 42)	T/χ^2	df	p
Maternal Age M (SD)	29.75 (4.63)	30.69 (5.90)	-0.87	91	0.389
Marital Status			40.31	3	<.0001
% Married	2	62			
% Co-habiting partner	49	21			
% Non-co-habiting partner	35	12			
% No partner	14	5			
Length of current relationship in months M (SD)	42.67 (47.58)	80.33 (57.09)	-3.47	91	.001

Ethnicity			5.26	5	.385
% NZ European	66	60			
% Maori	18	14			
% Other European	6	7			
% Asian	0	7			
% Pacific Island	0	2			
% Mixed Ethnicity / Other	10	10			
Schooling					
% Without formal schooling	78	33	28.39	6	<.0001
Finances					
% Unemployed	98	60	21.89	1	<.0001
% In receipt of a benefit	94	31	40.72	1	<.0001
Accommodation			13.55	5	.019
% Own home	16	48			
% Rented Private landlord	55	34			
% State owned house / flat	21	9			
% Living with family	8	9			

2.3 Procedures

A flow diagram is presented below to help illustrate the procedure and timing of measures used in the current study.



* One woman in the Methadone Maintenance Group gave birth to twins

** Three methadone exposed infants unable to be assessed

Figure 1

Timeline of Procedures and Measures Used in the Current Study

2.3.1 Recruitment and Consent

As described in the earlier section, recruitment of women in the methadone group was completed by the research nurse during the women's routine antenatal visits at the hospital Methadone in Pregnancy Clinic while recruitment of control women was completed with

randomly selected controls during their third trimester of pregnancy. Additional information was provided and consent sheets were signed at recruitment. A copy of the written information package provided for the pregnant women being recruited and the consent form used is attached in Appendix 3.

2.3.2 Maternal Interviews

Following recruitment and consent a comprehensive maternal interview was conducted with each pregnant woman towards the end of the third trimester of her pregnancy (post 33 weeks gestation). Interviews of the women involved in the methadone maintenance group were primarily conducted by the research nurse during the women's routine antenatal visits while pregnant women in the control group were interviewed by the author in the women's own homes. Maternal interviews took approximately one hour to one and a half hours to complete. A copy of the complete Maternal Interview is attached as Appendix 4.

2.3.3 Collection of Infant Clinical Characteristics

At the birth, clinical data on the newborn infant was collected. These measures were initially taken by the delivery team attending the birth and then validated by the team's research nurse. Further clinical information such as duration of stay in hospital and treatment for neonatal abstinence syndrome were collected throughout the infant's hospital stay.

2.3.4 Neurobehavioural Assessment

2.3.4.1 NNNS Assessment

Following delivery, mothers were contacted by the neurobehavioural assessor in order to arrange a time and place suitable to administer the assessment. Neurobehavioural assessments were scheduled to be conducted on all infants between 39 and 46 weeks gestation using the NICU Network Neurobehavioural Scale (NNNS). As much as possible assessments occurred around 42 weeks gestation (i.e. two weeks of age if the infant was

born at term). Experienced assessors have recommended that earlier assessments may prove difficult to administer and do not necessarily provide as clear an indication of the infant's best performance while elements of later assessments (e.g. primitive reflexes) may be skewed by the natural development of the infant. On occasions where an infant was totally unable to be assessed (for example, the infant was unable to regulate his/herself and maintain an appropriately responsive state), the assessors would reschedule with the infant's caregiver, up to three (and occasionally four) attempts in order to complete the assessment and as far as possible to elicit the infant's "best performance". This persistence means that a small number of infants were assessed after 43 weeks (n = 11). If an infant was still unable to be assessed after several separate attempts, endeavours to complete the NNNS assessment were abandoned and the infant was deemed "unable to be tested" (n = 3).

2.3.4.2 Cry Collection

In addition to administering the NNNS, a recording of a sub-sample of infant cries was collected during the NNNS assessment. At the conclusion of Section C of the NNNS exam ("Unwrap and Supine") infants were administered the NNNS item referred to as "tactile stimulation of the foot". While the infant was in the supine position a lapel microphone (Sony ECM-T145) was positioned approximately 15cm from the infant's mouth. The microphone was attached to a minidisk recorder (Sony M2 N710). If the administration of this item did not elicit a cry, the recording device was left running and a note was taken regarding when the infant began to cry. The current sampling methodology has similarities to past acoustic studies of infant crying (Nugent, Lester, Greene, Wieczorek-Deering & O'Mahony, 1996). In part, this procedure was chosen because it was less-invasive and therefore less likely to elicit refusal from parents or impact retention rates for follow-up studies.

2.4 Measures Used in the Current Study

2.4.1 Prenatal Drug Exposure

2.4.1.1 Methadone Exposure

Information on maternal methadone dose was gathered from the Methadone in Pregnancy Clinic of the CADS Methadone Maintenance Programme. Consent obtained from each woman enabled charts from the clinic to be photocopied and used by the research group. Using this information, average dose per trimester and average dose per total period enrolled in the Methadone Maintenance Programme were calculated for each woman. Figure 2 provides a histogram illustrating the distribution of methadone dosages from all three trimesters and overall mean methadone doses (calculated across all three trimesters) taken by the women in the methadone maintenance group during pregnancy.

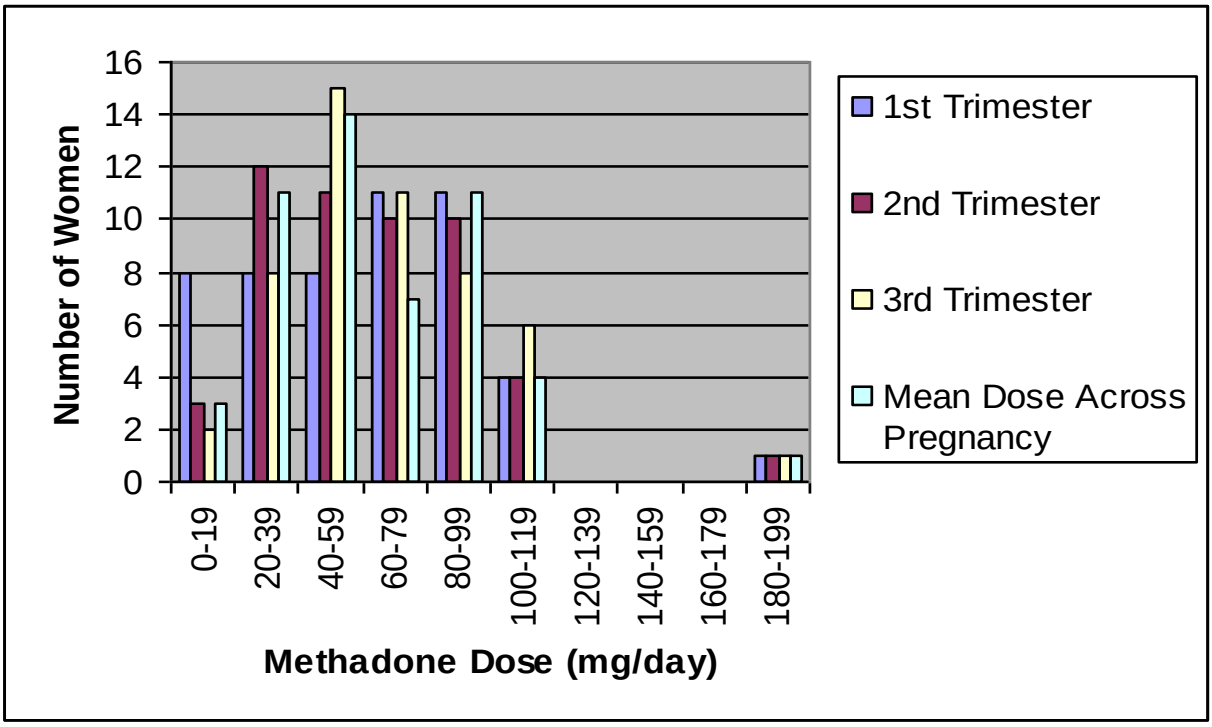


Figure 2
Maternal Methadone Dose Distributions

In order to examine the role of maternal methadone dose on infant outcome, study infants were divided into three groups based on maternal methadone dose during trimester three. Dose at trimester three was chosen for several reasons. First, it has been frequently used as the defining dose variable in previous literature (Chasnoff et al., 1984; Hagopian et al., 1996). Second, information on dose at trimester three was available for all women (where some women were not enrolled in the methadone maintenance programme for trimester

one). Third, although it is still unclear exactly how early methadone transfer begins to occur to the foetus it is known that transfer occurs at increasing levels over the gestation period (Kandall et al., 1999). Therefore, it has been suggested that dose levels during trimester three may be particularly important.

The mean dose across the group at trimester three was slightly higher at 62.28 mg/day (*SD* = 32.07) than the overall mean of 58.98 mg/day (*SD* = 33.33), with a median of 60 mg/day and a range of 11.2 mg/day to 195 mg/day. Further analysis suggested that overall dose measures and dose at trimester three were highly and significantly correlated ($p < .0001$).

For dose comparisons the methadone exposed group was divided using a median split with infants born to those women on 60 mg/day and below being grouped as "Low Dose" (n = 26), and above 60 mg/day being grouped as "High Dose" (n = 25). This dose level is relatively close to the mean dosages discussed in more recent New Zealand and international studies (Kuschel et al., 2004; McCarthy et al., 2005; Wouldes, 2004).

2.4.1.2 Exposure to Other Drugs

Prenatal exposure to other drugs was collected via self report during the Maternal Interview. A comprehensive section on maternal drug use, both licit and illicit was included. The questions around drug use utilised in the current study were based on those previously used in the widely acknowledged long-term epidemiological Christchurch Health and Development Study (Bowden, Fergusson & Horwood, 2006). The information in the drug use section focused mainly on use during the current pregnancy (broken down across the three trimesters) but also covered maternal use prior to the current pregnancy. Detailed questions regarding use were asked about cigarettes, cannabis, alcohol, benzodiazepines, heroin and other opiates (excluding methadone) and stimulants (e.g. speed, amphetamines, cocaine). For example, participants were asked how many cigarettes they smoked per day prior to pregnancy, during the first three months of pregnancy, during the second three months of pregnancy and during the final three months of pregnancy. The complete breakdown of questions is provided in Sections E and G of the Maternal Interview attached in Appendix 4.

2.4.2 Infant Clinical Measures

Clinical information collected at the infant's health and well being at birth included:

1. Infant gender.
2. Gestational age (provided in weeks/days and converted to a decimal system for analysis).
3. Birth weight (gms).
4. Birth length (cm).
5. Head circumference (cm).
6. Total length of stay in hospital following delivery (days). Information on this was also collected in finer detail for instance in regards to length of stay in Neonatal Intensive Care Unit (NICU).
7. Infant APGAR Scores (at one, five and ten minutes).

Additionally, for those infants born to women on the methadone maintenance programme and for those infants that required treatment for neonatal abstinence syndrome:-

8. Finnegan scores (Finnegan, Kron, Connaughton & Emich, 1975). This is a brief semi-objective assessment measure which examines the newborn for symptoms of NAS. (A copy of the exact measure used in the current study is attached in Appendix 5.)
9. Number of days on treatment
10. The type of treatment used.

2.4.3 Neurobehavioural Measures

2.4.3.1 NICU Network Neurobehavioural Scale

The NICU Network Neurobehavioural Scale (NNNS) is a relatively new measure developed by the National Institute of Health (NIH) specifically designed to evaluate the neurobehavioural profiles of at-risk infants, in particular infants prenatally exposed to drugs (Lester & Tronick, 2004). Developed through a process of revisions, amalgamations and additions to earlier neurobehavioral assessments such as Brazelton's Neonatal

Behavioural Assessment Scale (NBAS) and Finnegan's Neonatal Abstinence Scoring System, the NNNS is a comprehensive assessment of neurological integrity, which utilises a combination of observed and elicited behavioural functioning, and stress/abstinence symptomatology. Neurobehavioural functioning is examined using empirically validated methods such as assessing the infants muscle tone (both passive and active), primitive reflexes (for example the rooting and stepping reflexes), orientation abilities (both animate and inanimate) and ability to self regulate, while the stress/abstinence scale comprises symptoms that have been clinically documented as signs of neonatal abstinence.

Procedurally the NNNS assessment is a non-invasive measure that takes approximately 30 minutes to administer and can be used to assess any infant between the ages of 30-46 weeks gestation. The infant is assessed and scored on 115 individual items across three components: the examination itself (items 1-45), examiner observations of the infant (items 46-65) and a stress/abstinence scale (items 66-115). The physical examination itself follows a relatively invariant administration order, with items administered in eleven focused, state-dependent "packages" that the infant is moved through, for example, package "E" examines the infant's "upper extremities and face" while package "F" examines the infant's "upright responses". Packages are designed to reduce unnecessary manipulation while steadily moving the infant through the assessment following the infant's natural progression of state changes from sleep to wake. Standardised directions are also provided in regards to the context in which the assessment should take place and procedures to be followed in difficult situations, for example, a set procedure is outlined and required to be followed if or when an infant begins to cry.

In order to facilitate interpretation and enhance objectivity a detailed scoring guide accompanies the assessment. This includes descriptions, pictures, asymmetrical options and optimal scores (for the examination component). The assessor must choose the score that represents the infant's best performance on each item. In the event that an item is not administered specific codes are used to identify the reasons that the item was unable to be scored. For example a "99" represents examiner error while a "98" indicates that the infant was in an inappropriate state to complete the item. Observed stress/abstinence symptoms

are scored on a comprehensive "yes/no" checklist. For further details the complete scoring guide to the NNNS is available online at http://pediatrics.aappublications.org.

Tallied scoring of the NNNS provides information on twelve summary scores that can then be used for interpretation purposes. These include measures of: Habituation, Attention, Handling, Quality of Movement, Regulation, Non-optimal Reflexes, Stress/Abstinence, Arousal, Excitability, Hypertonicity, Hypotonicity and Lethargy. Development of themed summary scores was undertaken by the authors of the NNNS using a "combined conceptual and statistical (co-efficient alphas) aggregation of items and scores" (p. 185, Lester & Tronick, 2004). Basing summary scores over several items throughout the assessment is considered to enhance the reliability of the summary scores.

Initial reliability and validity of the NNNS was checked during the development of the Maternal Lifestyles Study in which 12 examiners across four sites assessed 1,400 one-month old infants from a variety of substance exposures, ethnicity, regions and social classes. Results showed that the NNNS reliably differentiated between drug exposed and control infants. Since its development several other studies have also used the NNNS, confirming both its reliability and validity (Boukydis, Brigsby, & Lester, 2004; Tronick et al., 2004). Reliability evaluation of the summary scores has shown adequate to good internal consistency, with alpha co-efficients ranging from 0.56 to 0.85 (Lester et al., 2004).

The majority (80%) of NNNS assessments were administered by one of two trained assessors (the author and the neonatal physiotherapist from Christchurch Women's Hospital). For most of these assessments the assessors worked together with one administering the assessment while the other observed. This kept procedures consistent across the assessors and was felt to enhance scoring validity as both assessors were able to report on what they observed. Whenever possible the NNNS assessment was performed within the hospital setting. When this was not possible assessments were performed at the infant's home. In order to avoid scoring biases, both NNNS administers were blind to maternal dose and any infant medications. An additional nineteen NNNS assessments (20%) were included that had been conducted by the previous NNNS assessor employed

by the larger study. This earlier assessor had been trained by the same instructor as the two primary assessors.

Quality of assessment procedures and inter-rater reliability of NNNS assessments were checked in June 2004 by a certified NNNS trainer. In order to enhance reliability and identify any potential biases that may have been occurring the trainer was blind to both maternal and infant exposure status. Reliability was assessed by comparing independent scoring of both videotaped and live assessments. Reliability conformed to criteria suggested in Lester et al. (2004). This indicates "no more than a two-point difference was found on items with >9 scale points, and for items with <5 scale points, agreement had to be exact with no more than five disagreements" (Lester et al., 2004, pp677).

2.4.3.2 Cry Measures

Consecutive vocalisation recordings from a large sub-sample of infants were undertaken during the NNNS assessment. In line with previous acoustic cry studies and due to the fact that many infants did not cry at all or only "fussed" during the assessment, recordings were subjected to a cry criterion in order to be included in later cry analyses. Grau, Robb & Cacace (1995) defined a crying episode as the uninterrupted crying activity that begins following administration of a cry-eliciting stimulus and continues to the eventual cessation of crying. To meet criteria for the current study, a crying episode had to be perceived as a high intensity period of distressed vocalisation sustained for a minimum of 15 seconds. Based on this definition a smaller sub-sample of ten infants from each group whose crying episode met these criteria was used for cry analyses.

On the basis of each infant's episode of crying, a series of cry utterances were identified. Lester et al., (2002) defined a cry utterance as an individual segment of crying that occurs during the expiratory phase of respiration. A cry utterance typically lasts for a period of 500 msec or longer. The present study extended this definition to only include cry utterances that only occurred upon exhalation, contained clear harmonic structure, and persisted for at least on second or longer. Based on information provided about typical infant cries and a review of the definitions used in previous cry studies (Hopkins, 2000)

this definition was assumed to provide the least ambiguous approach to identifying and acoustically measuring moments of crying. A total of five cry utterances were considered in the acoustic analysis of each infant.

Prior to acoustic analysis, each crying episode was converted to a "*wav*" file using a commercially available software package (Acoustica 3.2). Each *wav* file was then imported to a signal processing system (PRAAT 4.3.12). Cry utterances were then measured using a combination of amplitude-by-time displays and narrow band spectrographic displays. A narrow band spectrographic analysis involves a detailed analysis of the entire acoustic spectrum of the cry signal in intervals of 45 Hz. The outcome of this analysis results in a cry spectrogram which provides a representation of the F_0 of the cry signal and the associated harmonic components of the cry. Appendix 6 provides a visual illustration of the computer generated *wav* files of the infant utterances that were chosen for analysis after meeting the applied criteria. Pictorially this may be helpful in aiding the reader or future researchers wishing to replicate the current research in distinguishing cries that meet the criteria described.

On the basis of the spectrographic displays, two acoustic measurements were made:

1. Cry duration: Defined as the total time elapsed between the onset and offset of each cry utterance. Cry duration was measured (in msec) by superimposing a pair of vertical cursors at the onset and offset of acoustic energy summation of each cry utterance.
2. F_0: Defined as the lowest frequency component (in Hz) of the cry utterance. Measurements of F_0 were made manually over increments of 0.1 second across the duration of each cry utterance.

On the basis of the cry F_0 measures a number of statistical calculations were performed:

3. Mean F_0: An average of the incremental 0.1 second measures for each cry utterance.
4. F_0 SD: The standard deviation of the F_0 measures for each cry utterance.
5. The coefficient of variation: The standard deviation divided by the mean of each cry. This represents a general measure of variability between the two data sets.
6. Jitter Factor: A measure of F_0 perturbation (variability). As defined by Baken (1987) the jitter factor is "the mean difference between the frequencies of adjacent cycles

divided by the mean frequency, multiplied by 100" (p. 175). The equation to calculate jitter factor taken from Baken (1987, p175) is provided below:

$$\text{Jitter Factor} = \frac{\frac{1}{n-1}\left[\sum_{i=1}^{n-1} |F_i - F_{i+1}|\right]}{\frac{1}{n}\sum_{i=1}^{n} F_i} \times 100$$

7. Percentage of jitter directionality change: The number of times a frequency shift changes direction i.e. when the algebraic sign changes direction.
8. Melody contour: An approximation of the general pattern of F_0 of each cry (i.e. rising, falling or flat). This was assessed by fitting a first-order polynomial (i.e. linear regression) to the F_0 measurements.

2.4.4 Additional Measures

Information on confounding variables and maternal characteristics were taken from self reported answers to questions in the maternal interview and supplemented with information available on hospital records. The maternal interviews conducted were developed as part of the larger study by the previous research group co-ordinator and the primary investigator prior to the author's (ZQ) involvement in the research group. The interview questionnaire contained a combination of custom written questions with a number of structured questionnaire measures. Interviews included a large cross section of information with the aim of providing a comprehensive understanding of the environmental context and influences faced by each group. Information collected included maternal demographics, maternal well-being, important perinatal details (e.g. previous pregnancies, type of antenatal care) and a brief personality questionnaire. (Given the scope of the current thesis, only specifically selected information from the maternal interviews has been presented and used. More in-depth reporting of the information collected at maternal interview will be available in future reports and follow-up studies currently under way by the research group.) Attached as Appendix 4 is a copy of the complete Maternal Interview.

2.4.4.1 Maternal Background Characteristics

This information included details such as maternal age, ethnicity, education level, living arrangements, partner relationships and income. The majority of maternal characteristics (ethnicity, education level, living arrangements and partner relationship) were collected using a scaled check-box approach where the most applicable answer was circled. For example education level was graded on a seven point scale where; "1 = Left school between 13-16 years, no qualifications", "2 = School Certificate (>2 subjects)", "3 = Further secondary education, eg UE, HSC or Bursary", "4 = Secretarial or trade qualifications", "5 = Professional qualifications without a degree", "6 = University degree" and "7 = Other qualifications, describe _____". Income information was gathered via a number of questions, for example "Are you working (in paid employment) at the moment?", "How much do you receive each week after tax?", "How much do you receive in benefit payments per week?" For a more detailed understanding of the questions asked to establish maternal background characteristics see Sections A and C of the Maternal Interview attached as Appendix 4.

2.4.4.2 Maternal Nutritional Information

Maternal nutritional intake was established using a "servings per week" approach. Each woman was asked to calculate how many servings of fruit, vegetables, meat, bread, carbohydrates, milk and eggs she had eaten per week during pregnancy. For each of the food groupings, definitions were provided and example serving sizes were given, for example, "Fruit including fresh, frozen, canned, and stewed. 1 serving = 1 apple or 2 small apricots". A complete list of definitions and serving sizes are provided in Section D of the Maternal Interview attached as Appendix 4.

2.4.4.3 Maternal Well-being

Data on maternal well-being included questions relating to both maternal physical and mental health. Self report information provided by each woman was then supplemented and checked against available hospital records. An extensive list of maternal health

questions were asked including any history of epilepsy, hepatitis, diabetes, high blood pressure, thyroid trouble, anaemia and current or past psychiatric illness. The majority of these were answered using a dichotomous yes/no selection. Where applicable, such as with mental health diagnoses, additional details such as treatment or current medication were inquired about. Again, these are included in the Maternal Interview attached as Appendix 4.

2.5 Data Analysis

The majority of statistical data analysis was conducted using SPSS 14.00 for Windows. Clinical data and NNNS assessment results were entered directly into SPSS while Maternal Interviews were entered into Access then converted to SPSS for analysis and Cry Measurements were entered onto Excel and then converted to SPSS for analysis. (Data analysis to ascertain the summary scores of the NNNS assessment was executed using syntax files for SPSS specifically designed for use with the NNNS assessment by the Maternal Lifestyles Study provided by the author of the NNNS.)

Power for the current study was considered sufficient, based on the information that a large effect size (ES = 0.8) requires a sample size of 26 (n = 26) in order to obtain 80 percent statistical power. Bivariate analytic techniques were used to examine between group differences on each of the infant outcomes specified. For continuously distributed variables, two tailed independent samples t-tests were used, whilst for dichotomous variables, chi-square tests were used. Analyses of dose measures were conducted using univariate one-way analysis of variance (ANOVAS). . Where applicable the Levenes test was used to determine homogeneity of variance between the two groups. All tests were initially conducted using the ninety-five percent confidence level (i.e. a significance level of $p < .05$). These statistical tests were chosen for their functionality and simplicity. Additional information on further statistical analyses, including any more refined or alternative procedures, is specified in the results section.

Results

3.1 Layout and Organisation of the Results Section

The results section of this thesis is divided into three sections, as guided by the aims of the research described at the end of the introduction. The first section compares the clinical and neurobehavioural characteristics (NNNS scores followed by analyses of infant cry) of the methadone exposed infants with the non-methadone exposed control comparisons. The second section examines the association between maternal methadone dose during pregnancy and infant outcomes. This begins with a reiteration of the maternal dose groupings and is followed by the presentation of between-group findings, across "no dose" (non-methadone exposed control comparisons) "low dose" and "high dose" groups, for clinical and neurobehavioral (NNNS score) measures. The final section of the results, examines the roles of confounding variables and their influence on the data examined in the earlier sections.

Note: One woman on the Methadone Maintenance Group had twins therefore infant sample size for the Methadone Exposed Group is 51 while maternal sample size is 50.

3.2 Section 1: Between Group Comparisons of Clinical and Neurobehavioural Characteristics: Methadone Exposed Infants and Non-Exposed Comparison Infants

3.2.1 Clinical Characteristics of Methadone Exposed and Non-Exposed Comparison Infants

Table 4 compares the clinical characteristics of the infants exposed to methadone during pregnancy and comparison infants not exposed to methadone during pregnancy. Between-group comparisons were tested for significance using the chi squared test of independence for dichotomous variables (presented in percentages) and independent samples t-tests for continually distributed variables (presented with means and standard deviations).

The results presented in Table 4 reveal the presence of significant differences between the two groups on measures of infant birth weight ($p < .0001$) and head circumference ($p < .001$) with infants exposed to methadone during pregnancy found to be significantly lighter with smaller head circumferences. There was also a tendency for those infants exposed to methadone during pregnancy to be slightly shorter at birth ($p = .093$).

The two groups of infants also differed significantly across Finnegan's scores ($p < .0001$), treatment for neonatal abstinence syndrome ($p < .0001$) and days in hospital ($p < .0001$) with a large number of the methadone exposed infants requiring treatment for neonatal abstinence syndrome and more likely to spend longer in hospital. Notably, the mean stay of the methadone exposed infants in hospital was 18 days ($SD = 13.40$) with a range of four to 77 days, while in contrast, the non-methadone exposed comparison infants had a mean stay of three days ($SD = 1.82$) with a range of no days to seven days.

No significant differences between the two groups were found on measures of infant gender, gestational age at birth, frequency of preterm (<37 weeks) birth or infant APGAR scores at both one and ten minutes.

Table 4

A Between Group Analysis of the Means (M) and Percentage (%) Values of Infant Clinical Characteristics for Infants Exposed to Methadone During Pregnancy and Non-exposed Comparison Infants. Standard Deviations provided in Parentheses

Clinical Measure	ME (n=51)	Control (n=42)	t/χ^2	df	p
% Male	51 (n=26)	48 (n=20)	.10	1	.747
M Gestn (wks)	38.82 (1.79)	39.22 (2.12)	-.99	91	.326
% Preterm (<37 wks)	8 (n=4)	2 (n=1)	1.35	1	.245
M Birth Weight (gms)	2,963.04 (506.75)	3,478.21 (562.49)	-4.64	91	<.0001
M Birth Length (cm)[§]	49.98 (3.45)	51.67 (6.00)	-1.70	90	.093
M Head Circ. (cm)[§]	33.60 (2.09)	34.81 (1.26)	-3.42	90	.001

M Days Hospital	18.20 (13.40)	2.76 (1.82)	8.06	90	<.0001
M 1min APGAR[a]	8.22 (1.56)	8.30 (1.42)	-.13	90	.894
M 10min APGAR[a]	9.90 (0.36)	9.81 (0.67)	.82	90	.414
M Highest Finnegan[¥]	13.40 (3.46)	0 (0.00)	27.35	89	<.0001
% NAS treatment	86 (n=44)	0	68.77	1	<.0001

[a] One infant was a home birth no APGAR scores collected.

[§] One infant missing data on length and head circumference.

[¥] Two infants missing data on Finnegan's Score

3.2.2 Neurobehavioural Characteristics of Methadone Exposed and Non-Exposed Comparison Infants

3.2.2.1 Analyses of NNNS Outcomes

The following section presents the results of infant neurobehavioral integrity assessed using the NICU Network Neurobehavioural Scale (NNNS). Prior to analysis of summary scores, independent sample t-tests were run in order to ascertain any differences between the testing ages of the two groups of infants. Analysis was conducted in regards to both gestational age and corrected age (i.e. actual age in whole days since birth). At the time of neurobehavioural assessment the mean gestational age of the methadone exposed infants was 52 days old (*SD* = 13.00), while the equivalent mean was 54 days (*SD* = 10.64) for the controls infants. Means for actual age at time of assessment was 20 days (with a range of 2 to 78) for the methadone exposed infants and 16 days (with a range of 4 to 38) for the control infants. Both tests showed that there were no significant differences between the two groups at time of testing (gestational age: $t(87) = -.520$, $p = .604$; actual age: $t(87) = 1.391$, $p = .168$).

Table 5 shows sample numbers, means and standard deviations of the summary scores of the NNNS for methadone exposed and non-exposed infants. Summary scores for the NNNS assessment were computed via a SPSS syntax file which accompanied the assessment measure as provided by the author (Lester & Tronick, 2004). This syntax calculates the infant's performance across relevant individual items in order to obtain

summary scores as explained in the methods section. Between group differences were assessed using the independent samples t-test for each summary score.

Sample numbers for each of the summary scores differ due to infant state and the related inability to perform aspects of the NNNS assessment when the infant is in an inappropriate state (as explained in the Methods section). If an infant was still unable to be assessed after four separate attempts, endeavours to complete the NNNS assessment were abandoned. Based on these criteria, three of the methadone exposed infants were unable to be assessed, two of the methadone exposed infants took four attempts, six took three attempts, eight took two attempts and 32 took one attempt. In contrast, one non-exposed control infant took three assessment attempts to assess, seven took two attempts and 34 took one attempt. When tested statistically, these differences between the two groups, in regards to number of attempts required to complete the NNNS assessment, were insignificant ($\chi^2(4) = 7.902$, $p = .095$). It is important to note that the results presented below do not include any data obtained from the three methadone exposed infants that were unable to be assessed.

Examination of the neurobehavioural profiles showed that significant differences occurred across the large majority of the NNNS summary scores. Namely there were significant differences across NNNS Habituation, NNNS Attention, NNNS Handling, NNNS Quality of Movement, NNNS Regulation, NNNS Non-optimal Reflexes, NNNS Stress/Abstinence, NNNS Arousal, NNNS Excitability and NNNS Hypertonicity. (Summary scores that were not statistically significant were NNNS Lethargy and NNNS Hypotonicity.) For each of the summary scores, the higher the score, the more the infant reflects that characteristic.

The summary scores on which the two groups of infants differed the most were NNNS Quality of Movement, NNNS Regulation, NNNS Stress/Abstinence and NNNS Excitability. NNNS Quality of Movement is a measure of smoothness of movement and motor control. Mean scores on the NNNS Quality of Movement summary item were significantly higher for the non-methadone exposed control group in comparison to the methadone exposed group ($p < .0001$) indicating that the non-methadone exposed control infants displayed significantly smoother movements and better motor control. Likewise non-methadone exposed control infants scored higher than their methadone exposed

counterparts on the summary score of NNNS Regulation ($p < .0001$). This summary score is among the most global and reflects how well the infant was able to cope with the assessment and settle his or herself. The higher scores obtained by the non-methadone exposed control infants reflects that they were better able to do this. Not surprisingly, the methadone exposed group displayed a significantly higher group mean on the NNNS Stress/Abstinence summary score ($p < .0001$) indicating that the methadone exposed infants displayed more signs commonly representative of neonatal abstinence and stress, for instance tremors, startles and rapid changes of skin colour. The methadone exposed group of infants also displayed a significantly higher mean NNNS Excitability summary score ($p < .0001$). This summary score is a measure of infant reactivity that takes into account physiological aspects of reactivity; therefore, this heightened mean indicates that the methadone exposed group were more sensitive during the assessment than their non methadone exposed control counterparts.

The six other significant summary scores were NNNS Habituation, NNNS Non-optimal Reflexes, NNNS Arousal, NNNS Hypertonicity, NNNS Attention and NNNS Handling. Sample sizes across the NNNS Habituation scores were low in both groups. This smaller number is likely to reflect the fact that the infant is required to be in a sleeping state at the beginning of the NNNS assessment in order for this part of the NNNS assessment to be administered. However, across the current numbers the mean NNNS Habituation score for the non-methadone exposed control group was significantly higher than that of the methadone exposed group ($p = .001$). This indicates the methadone exposed infants were slower and less able to progressively tune out intrusive noises compared to the control infants. In "real" terms, this indicates that the methadone exposed infants took approximately seven or eight trials to block out the noise of a rattle or bell while it took the non-methadone exposed infants three or four trials. Infants in the methadone exposed group were also found to have a higher mean on the summary score of NNNS Non-optimal reflexes, indicating a significantly higher number of sub-optimal reflexes ($p = .001$). The methadone exposed group had a significantly higher mean Arousal summary score ($p = .001$) indicating that this group of infants was quicker to fuss or cry during the administration of the NNNS assessment than their non-methadone exposed control counterparts. Methadone exposed infants also obtained a significantly higher mean across

the NNNS Hypertonicity summary score (p = .001) signifying that a higher proportion of the methadone exposed infants displayed notably heightened muscle tone in legs, arms and torso. NNNS Attention reflects the infant's ability to attend to auditory and visual stimulation. Those infants in the methadone exposed group had lower mean Attention scores than the non-methadone exposed control counterparts indicating a shorter or weaker ability to attend (p =.004). Finally, NNNS Handling is a measure of the amount of examiner support the infant needed during assessment to maintain an appropriately responsive state. Findings showed that methadone exposed infants required more support in comparison to the non-exposed group (p =.031) signifying that more assistance such as talking to the infant and picking the infant up was required by the assessor to keep the infants in the methadone exposed group in an appropriate state. Finally, there were no significant between group differences on summary score measures of NNNS Hypotonicity (notably decreased muscle tone) or NNNS Lethargy (sluggish or delayed responsivity).

Collectively these summary scores suggest that the methadone exposed infants were more reactive, showed less motor maturity, were less able to maintain themselves in an appropriate responsive state and displayed more signs of stress than their non-methadone exposed control comparisons.

As mentioned previously, the results presented do not include any data obtained from the three methadone exposed infants that were unable to be assessed. These infants were not assessed because they were overly reactive, generally unsettled and never in an appropriate state to administer the NNNS assessment. No infants in the non-exposed comparison group were unable to be assessed. Thus it is likely that the current analysis may to some extent underestimate any differences between the two groups.

Table 5

A Between Group Analysis of Infant Neurobehavioural Outcomes for Infants Exposed to Methadone During Pregnancy and Non-exposed Comparison Infants at Approximately 42 weeks Gestation

	ME (n = 48)	Control (n = 42)

NNNS Scale	n	Mean	SD	n	Mean	SD	t	df	p
Habituation	27	5.98	2.10	17	7.68	.90	-3.70	42	.001
Attention	34	5.93	1.63	37	6.95	1.11	-3.02	69	.004
Handling	40	0.31	0.30	41	0.17	0.25	2.19	75.43	.031
Quality of Movement	44	3.95	1.03	42	4.82	0.80	-4.39	84	<.0001
Regulation	45	5.31	0.93	42	6.26	0.80	-5.10	85	<.0001
Non opt. Reflexes	48	4.31	2.54	42	2.86	1.52	3.35	88	.001
Stress/Abstin	48	0.18	0.09	42	0.10	0.06	5.60	78.46	<.0001
Arousal	45	4.39	0.79	42	3.84	0.61	3.62	82.06	.001
Excitability	48	4.21	2.71	42	2.14	1.98	4.16	85.49	<.0001
Hypertonicity	46	0.57	0.90	42	0.10	0.37	3.38	62.29	.001
Hypotonicity	46	0.13	0.34	42	0.12	0.33	.16	86	.874
Lethargy	48	3.16	2.49	42	2.98	1.33	.46	73.71	.647

3.2.2.2 Analysis of Cry Characteristics

This section presents neurobehavioural findings relating to analysis of infant cry. As infant cry measures were taken during the assessment of the NNNS, analyses in regards to age at time of testing were unnecessary. As noted above, there were no significant ($p < .05$) differences between the two groups in regards to age at testing.

Forty-five cries meeting criteria were collected from the sub-sample of ten methadone exposed infants while 44 cries were collected from the sub-sample of ten comparison infants.

To evaluate differences between the cry characteristics of the two groups, a number of two-tailed independent samples t-tests were performed. The means and standard deviations of the cry characteristics, and the results from the t-tests run are provided in Table 6. Results of the t-tests revealed that there were significant between group differences across

all measures of frequency perturbation. Both jitter factor (p = .012) and jitter directionality (p = .015) were significantly different between the two groups. In both cases the methadone exposed infants had higher jitter values than the non-exposed control infants. In general the results of the jitter analyses were indicative of the infants in the methadone groups demonstrating more cycle-to-cycle variability in the vocal fold vibration of their cries. The coefficient of variation was also significant (p = .008), indicating that even at a more rudimentary level the methadone exposed infants had a higher level of overall variation than their non-methadone exposed comparisons. In order to illustrate this, examples of cry utterances containing a particularly stable F_0 and a particularly erratic F_0 are presented in Figure 3 and Figure 4 below.

T-tests run on the duration of infant cry utterance, mean F_0, F_0 standard deviation, and the melody contour of the infants' cries returned no significant results. This indicates that there were little or no differences across the measures of utterance duration of those infants exposed to methadone during pregnancy in comparison to non-methadone exposed control infants. There was also little or no difference between the two groups in regards to F_0 or the SD of the F_0. Finally, there was little or no difference between the melody contours (i.e. slope of the cry) between those infants exposed to methadone during pregnancy in comparison to non-methadone exposed control infants.

Table 6

A Between Group Analysis of the Mean Values of Infant Cry Characteristics for Infants Exposed to Methadone During Pregnancy and Non-exposed Comparison Infants with Standard Deviations Provided in Parentheses

Cry Characteristic	ME (n = 45)	Control (n = 44)	t	df	p
Utterance Dur (secs)	1.39 (0.44)	1.47 (0.47)	-.945	87	.347
F_0 (Hz)	508.00 (164.51)	494.71(244.37)	0.30	87	.764
SD of F_0 (Hz)	100.37 (78.44)	72.81 (84.21)	1.60	87	.114
Jitter Factor (Hz)	112.30 (82.77)	75.62 (45.62)	2.60	68.79	.012
% Directional Jitter	32 (14)	24 (14)	2.48	87	.015
Coefficient of	0.20 (0.12)	0.14 (0.08)	2.72	77.20	.008

Variation (Hz)					
Melody Contour	3.06 (15.86)	0.98 (9.53)	0.75	72.41	.453

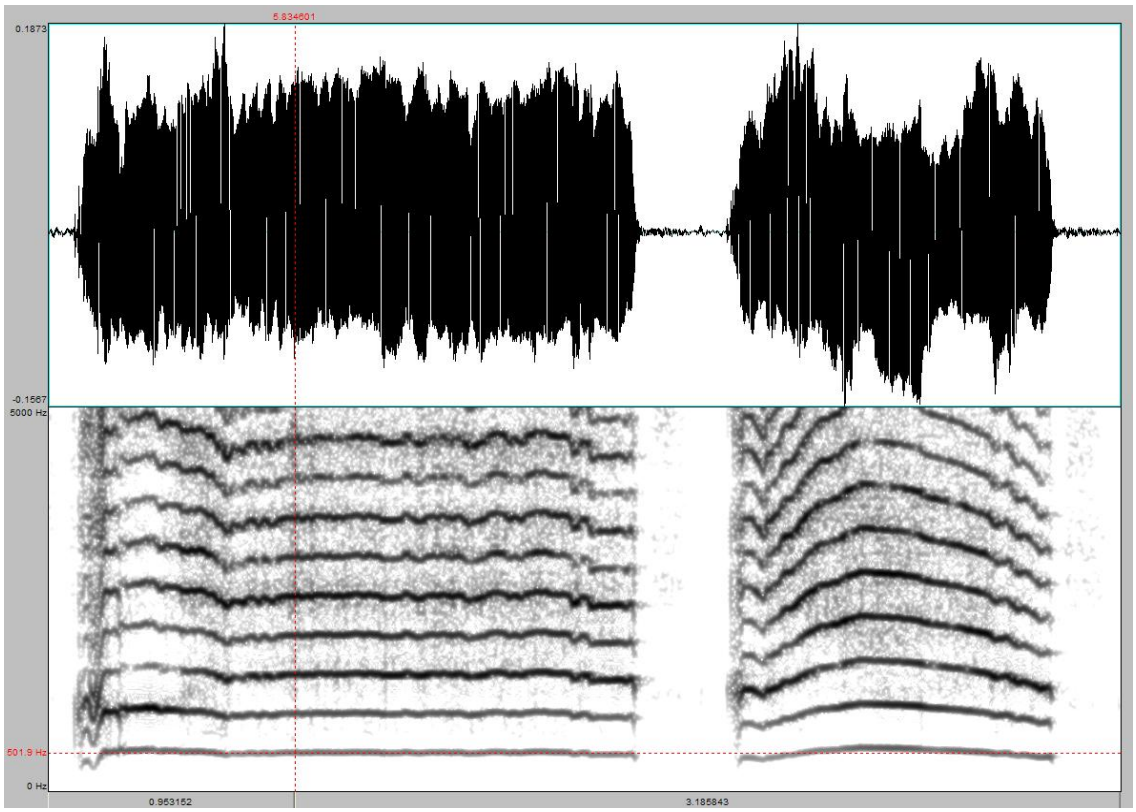


Figure 3
Example of an Infant Cry with Stable Fundamental Frequency (displaying low frequency perturbation). The top panel provides an amplitude-by-time display of two cry utterances. The bottom panel is a spectrographic representation of the same two cry utterances. Frequency (Hz) is depicted on the ordinate and time (sec) is depicted along the abscissa. The lowest horizontal line represents the F_0 with the associated harmonic components depicted above the F_0.

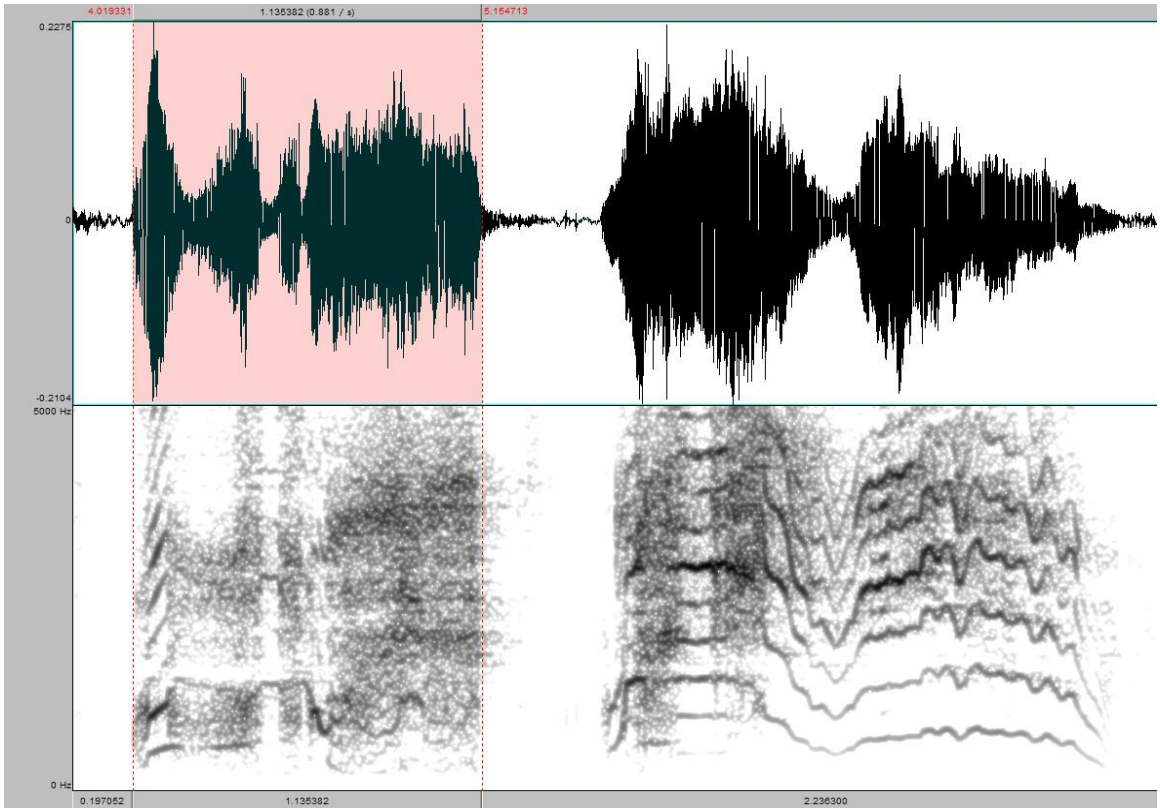


Figure 4

Example of an Infant Cry with Erratic Fundamental Frequency (displaying high frequency perturbation). The top panel provides an amplitude-by-time display of two cry utterances. The bottom panel is a spectrographic representation of the same two cry utterances. The lowest horizontal line represents the F_0 with the associated harmonic components depicted above the F_0.

3.3 Section 2: Examination of the Relationship Between Maternal Methadone Dose During Pregnancy and Infant Outcomes

3.3.1 Maternal Methadone Dose Distribution and Groupings

The findings discussed above suggest that there are significant differences across both the clinical and neurobehavioural profiles of methadone exposed infants in comparison to non-methadone exposed control infants. A further important issue in the literature related to methadone exposure in utero is that of maternal methadone dose. In order to examine this issue, the analysis was extended to examine the extent to which increased levels of

methadone exposure during pregnancy were associated with increased infant risk. As previously described in the Methodology Section (2.3.1.1) study infants were divided into three groups.

Grouping used a median split based on mean maternal methadone dose during trimester three. Infants exposed to maternal methadone doses of 60 mg/day and below were considered "Low Dose" (n = 26) while those exposed to maternal doses of greater than 60 mg/day were considered "High Dose" (n = 25). The group of control infants was referred to as the "No Dose" (n = 42) group as these infants were not exposed to methadone in utero.

3.3.2 Infant Clinical Characteristic Analysed by Maternal Methadone Dose During Pregnancy

Table 7 examines the relationship between infant clinical characteristics and maternal methadone dose. Between group differences were tested using the chi squared test of independence for dichotomous measures or one way analysis of variance for continuously distributed measures (ANOVA) with tests for linear trends. F statistics presented represent those for tests related to linearity.

As shown in Table 7 clear linear associations were found between the groups across the clinical measures of birth weight ($p < .0001$), birth length ($p = .022$), head circumference ($p < .0001$) and days in hospital ($p < .0001$). Increasing maternal methadone dose during pregnancy was associated with a higher risk of the infant being born lighter, shorter, having a smaller head circumference and having a longer stay in hospital. There were no significant ($p < .05$) non-linear trends found in the data. Tests for linear trends were also significant across Finnegan's Scores ($p < .0001$) and treatment of neonatal abstinence syndrome ($p < .0001$). However, it should be noted that these measures were also associated with significant non-linear trends ($p < .0001$). This violation is likely to be because no control infants were given Finnegan's scores or treated for neonatal abstinence syndrome.

Results that were not significant, included gestational age, rates of prematurity and infant APGAR scores at both one and ten minutes.

Table 7

Association between Maternal Methadone Dose During Pregnancy and the Means (M) and Percentage (%) Values of Infant Clinical Characteristics. Standard Deviations Provided in Parentheses

Clinical Measure	No Dose (n=42)	Low Dose ≤ 60mg/day (n=26)	High Dose > 60mg/day (n=25)	F/χ^2	df	p
M Gestation (wks)	39.22 (2.12)	39.17 (1.29)	38.47 (2.16)	2.13	1	.148
% Preterm (<37 wks)	2 (n=1)	4 (n=1)	12 (n=5)	2.58	1	.108
M Birth Weight (g)	3,478.21 (562.49)	3,115.00 (401.33)	2,805.00 (562.30)	26.81	1	<.0001
M Birth Length[§] (cm)	51.67 (5.99)	51.12 (3.01)	48.80 (3.54)	5.40	1	.022
M Head Circ.[§] (cm)	34.81 (1.24)	34.05 (1.17)	33.14 (2.70)	14.24	1	<.0001
M 1min APGAR[a]	8.26 (1.42)	8.16 (1.68)	8.28 (1.46)	0.00	1	.996
M 10min APGAR[a]	9.81 (0.67)	10 (0.0)	9.80 (0.50)	0.20	1	.887
M Days Hospital	2.76 (1.82)	15.85 (14.22)	20.75 (12.22)	56.07	1	<.0001
M > Finnegan[¥]	0 (0.00)	12.77 (3.53)	14.08 (3.34)	539.06	1	<.0001
% NAS Treatment	0	77(n=20)	96 (n=24)	63.77	1	<.0001

[a] One infant was a home birth no APGAR scores collected.

[§] One infant missing data on birth length and head circumference.

[¥] Two infants missing data on Finnegan's Score

3.3.3 Infant Neurobehavioral Outcomes Analysed by Maternal Methadone Dose During Pregnancy

3.3.3.1 Analyses of NNNS Outcomes

Table 8 describes the relationship between maternal methadone dose and infant neurobehavioural outcomes assessed using the NNNS. Analysis was conducted using the chi squared test of independence for dichotomous measures or one way analysis of variance for continuously distributed measures (ANOVA) with tests for linear trends. F statistics presented represent those related to linearity.

As before, preliminary analyses were conducted using a one-way ANOVA to check for differences across age at time of testing and number of attempts made. There were no significant ($p < .05$) linear trends across any of these factors. However, there was a significant difference between the groups across the number of attempts at assessment made ($F(2) = 11.290$, $p < .000$). When post hoc multiple comparisons were examined, these between-group differences lay between the low dose group and both the high dose ($p < .000$) and the no dose group ($p < .000$). This difference reflects a mean number of 2.19 ($SD = 2.19$) assessment attempts in the low dose group in comparison to a mean of 1.28 ($SD = .678$) for the high dose group and 1.21 ($SD = .470$) for the no dose group.

The results of Table 8 reveal strong associations between dose related exposure in utero and infants neurobehavioural performance on measures of NNNS Habituation ($p = .005$), NNNS Attention ($p = .007$), NNNS Quality of Movement ($p < .0001$), NNNS Regulation ($p < .0001$), NNNS Non-Optimal Reflexes ($p < .0001$), NNNS Stress/Abstinence ($p < .0001$), NNNS Arousal ($p < .0001$), NNNS Excitability ($p < .0001$) and NNNS Hypertonicity ($p < .0001$). The summary score of NNNS Handling also came close to significance ($p = .064$). These results signify that the higher the maternal methadone dose during pregnancy the harder the infant finds it to regulate his or herself, manifested in an inability to block out intrusive stimuli, and maintain focused attention to presented stimuli. Quantifiably, this means that high dose infants took almost twice as long as non-exposed comparisons to habituate to intrusive stimuli (nine presentations as opposed to five or six

presentation) and were less likely to be able to follow a ball for more than a 30 degree arc. An increase in maternal dose also relates to a more easily upset infant, going through more withdrawal symptoms with a more rigid yet less maturely developed musculature.

For the majority of neurobehavioural summary scores no significant ($p < .05$) deviation from linearity was returned. However, for both NNNS Stress/Abstinence ($F(1) = 5.11$, $p = .026$) and NNNS Regulation ($F(1) = 5.65$, $p = .020$) significant deviation from linearity was reported. This suggests these relationships do not follow a purely linear trend.

Neurobehavioural areas that were clearly not significantly different between the groups and returned no linear trends were again NNNS Hypotonicity and NNNS Lethargy.

Table 8

Association between Maternal Methadone Dose During Pregnancy and Mean Values (M) of Infant Summary Scores on the NNNS. Standard Deviations provided in Parentheses

NNNS Information	No Dose (n=42)	Low Dose ≤ 60mg/day (n=26)	High Dose > 60mg/day (n=25)	F	df	p
M Gestational Age at Testing	15.95 (8.26)	19.68 (13.45)	19.60 (17.03)	1.20	1	.277
M Actual Age at Testing	53.60 (10.64)	54.95 (13.03)	49.92 (12.76)	1.54	1	.218
M # of Assesst Attempts	1.21 (0.47)	2.19 (1.39)	1.28 (0.68)	.90	1	.346
M Habituation	7.68 (0.90)	6.12 (2.06)	5.89 (2.20)	8.59	1	.005
M Attention	6.95 (1.11)	5.96 (1.68)	5.90 (1.63)	7.88	1	.007
M Handling	0.17 (0.25)	0.32 (0.31)	0.30 (0.31)	3.53	1	.064
M Qual. Movt	4.82 (0.80)	4.18 (1.17)	3.72 (0.87)	21.93	1	<.0001
M Regulation	6.26 (0.80)	5.27 (0.93)	5.34 (0.94)	20.16	1	<.0001
M Non-opt. Reflexes	2.86 (1.52)	3.43 (1.83)	5.12 (2.85)	18.27	1	<.0001

M Stress/Abstin	0.10 (0.06)	0.18 (0.09)	0.19 (0.08)	24.42	1	<.0001
M Arousal	3.84 (0.61)	4.26 (0.82)	4.50 (0.76)	14.04	1	<.0001
M Excitability	2.14 (1.98)	3.48 (2.86)	4.88 (2.42)	21.52	1	<.0001
M Hypertonicity	0.10 (0.37)	0.36 (0.66)	0.75 (0.99)	14.86	1	<.0001
M Hypotonicity	0.12 (0.33)	0.09 (0.29)	0.17 (0.38)	0.22	1	.683
M Lethargy	2.98 (1.33)	3.30 (2.16)	3.04 (2.81)	0.41	1	.840

NB. Sample sizes range from 11 to 42. Sample size of 11 is for NNNS Habituation Low Dose Group.

Given the low sample size of the infant cry measure, cry analyses were not undertaken across maternal dose groups.

3.4 Section 3: Consideration of Maternal Lifestyle Factors Associated with Maternal Methadone Maintenance Treatment During Pregnancy

The preceding analyses have established that significant results do exist between the methadone exposed group and their non-methadone exposed control comparisons and that clear and pervasive dose responses also exist. However, before causal effects can be established it is important to consider whether these results are a direct reflection of methadone exposure during pregnancy or whether they have occurred due to confounding factors (unconsidered external factors) correlated with maternal methadone use. Therefore, confounding variables need to be factored into the analyses. In layman's terms, any influence from other factors that may be creating the differences between the two groups needs to be taken into account before any definite conclusions can be drawn.

Factors that were considered to be confounding variables included maternal drug use during pregnancy (other than methadone use), maternal nutritional intake during pregnancy and maternal health factors, including both physical and mental well being. These are all factors which have been raised in previous critiques as important yet often inadequately considered (Householder et al, 1982; Jacobson & Jacobson, 2005; Kaltenbach, 1994). Each of these factors is discussed below in further detail.

3.4.1 Maternal Drug Use During Pregnancy

It is a well acknowledge fact in the literature that a large minority of women on methadone maintenance programmes are polydrug users, and continue to use other drugs while undergoing methadone treatment (Lester et al., 2001 cited in Coles & Black, 2006). Initially a chi square analysis was undertaken in order to ascertain between group differences in drug use. This revealed that women in the methadone maintenance group were significantly more likely to have smoked tobacco (p <.0001), used marijuana (p <.0001), benzodiazepines (p <.0001) stimulants (p = .006), opiates (additional to methadone) (p <.0001) and Ritalin (p = .031) during their pregnancy. However, similar rates of alcohol use were reported across the two groups. Having found substantive differences across the two groups, drug use was further analysed across maternal methadone dose rates. Table 9 provides a list of drugs used during pregnancy and the percentages of each group that used each type of drug. Again, a chi square analysis was undertaken in order to ascertain between group differences.

An indication of poly-drug drug use was calculated by counting up the number of drugs a woman acknowledged using during pregnancy. (This measure is represented in Table 9 as Poly-drug Measure). Between group differences across this measure were calculated using one way analysis of variance. Based on the means displayed, poly-drug use did not appear to follow a linear trend. While the mean number of drugs used by the comparison women during pregnancy approximated one (in whole numbers), the mean of the *high* dose group approximated to two (in whole numbers) while the mean of the *low* dose group approximated to three.

Table 9

Maternal Drug Use During Pregnancy for Women Enrolled in Methadone Maintenance Treatment During Pregnancy and Comparison Women

Drug Type	No Dose (n=42)	Low Dose ≤ 60mg/day (n=26)	High Dose > 60mg/day (n=25)	F/χ^2	df	p
% Using Tobacco	31	100	92	44.33	2	<.0001
% Using Marijuana	5	46	40	17.97	2	<.0001

% Using Alcohol	29	31	16	1.76	2	.415
% Using Benzodiazepines	0	23	40	18.48	2	<.0001
% Using Stimulants	2	23	20	7.65	2	0.22
% Using Opiates (excluding Methadone)	0	42	20	30.37	2	<.0001
% Using Ritalin	1	7	2	7.98	2	.019
M (SD) Poly drug Measure	0.69 (1.02)	2.85 (1.35)	2.36 (1.35)	29.87	2	<.0001

N.B. Drug use was considered positive if it was acknowledged at any stage during pregnancy

3.4.2 Maternal Nutrition and Diet During Pregnancy

Another aspect of maternal lifestyle that is likely to affect foetal development in utero and therefore represents a confounding variable is maternal nutritional intake (diet) during pregnancy. Initially, independent samples t-tests were done to ascertain whether there were any differences between women enrolled in methadone maintenance treatment and the comparison women. This returned several significant results with women in the methadone maintenance group eating significantly less fruit ($t(91) = -3.64$, $p < .000$), vegetables ($t(91) = -4.36$, $p < .000$), carbohydrates (pasta, rice and cereal) ($t(72.07) = -1.33$, $p < .000$) and drank less milk ($t(91) = -2.41$, $p = .018$) than the control women. Most notably, they ate almost half the number of vegetables and half the amount of bread when compared to the comparison women. Given these differences a between group one way analysis of variance was undertaken to examine if these differences lay primarily with either the low dose group or high dose group.

Table 10 presents the average number of weekly servings of food types eaten per week throughout pregnancy divided into maternal dose groupings. Post-hoc multiple comparisons on the one way ANOVA revealed that all significant ($p < .05$) differences lay between the controls and the methadone exposed group. With no differences evident between the low and high dose methadone groups.

Table 10

Analysis of Maternal Nutritional Servings Throughout Pregnancy Based on Maternal Self-Report Comparisons Across Maternal Methadone Dose During Pregnancy. Standard Deviations provided in Parentheses

Food Type (Serves per wk)	No Dose (n=42)	Low Dose ≤ 60mg/day (n=26)	High Dose > 60mg/day (n=25)	F	df	p
Fruit	15.57 (8.58)	11.50 (9.40)	7.48 (3.83)	8.35	2	<.0001
Vegetables	15.43 (7.42)	9.46 (8.97)	7.84 (5.57)	9.75	2	<.0001
Meat	7.74 (4.95)	7.00 (3.10)	5.60 (2.22)	2.37	2	.100
Bread	22.71 (15.04)	13.19 (6.76)	11.44 (7.24)	9.72	2	<.000
Carbohydrates	9.31 (6.33)	7.31 (3.38)	8.24 (5.47)	1.12	2	.330
Milk	13.67(12.91)	9.54 (8.45)	7.56 (5.49)	3.12	2	.049
Eggs	2.76(3.15)	2.65 (2.98)	3.88 (2.95)	1.28	2	.284
Total Servings	87.19 (27.98)	60.65 (25.96)	51.88 (15.32)	18.87	2	<.0001

3.4.3 Maternal Health – Physical and Mental Health

Maternal health was also considered in regards to infant development in utero. Health was considered in regards to both physical and mental well being. Physical health measures included, but were not limited, to items such as heart disease, asthma, diabetes and hepatitis. (A full listing of these is supplied in Appendix 4.) Maternal physical well being was calculated by taking a tally of how many of these factors featured in the history of each pregnant woman. Maternal mental health was taken as past or current history of diagnosed mental illness. Table 11 illustrates the differences between the two groups in regards to maternal health. Differences in physical health were established via a one way analysis of variance, while differences in mental health were analysed using a chi square test. Significant differences occurred across both measures of maternal health. Post hoc comparisons on the one way analysis of variance again revealed that these differences existed solely between those women enrolled in the methadone maintenance programme and the control women (and not between the low and high dose methadone groups).

Table 11

Associations Between Measure of Maternal Health and Maternal Methadone Dose During Pregnancy. Standard Deviations provided in Parentheses

Maternal Health Measure	No Dose (n=42)	Low Dose ≤ 60mg/day (n=26)	High Dose > 60mg/day (n=25)	F	df	p
M Physical Health	0.48 (0.79)	1.50 (0.99)	1.88 (1.05)	21.74	2	<.0001
Mental Health	19	58	48	13.22	4	.010

NB. Information on the mental health of two control women was not obtained

3.4.4 Analyses of Between Group and Dose Related Differences When Considering Related Maternal Lifestyle Factors

In order to consider the influence of maternal lifestyle factors on the differences observed between the groups, as presented in the earlier analyses, a linear regression model was used. Several steps were involved in this process. Initially, a correlation matrix was run. The purpose of this matrix was twofold: one, to ensure that variables entered into the regression model were indeed correlated with the dependent variable being tested; and two, to examine any large overlaps between co-variate variables that would mean having both variables entered into the model would make them redundant. Only one large overlap of this type was found this overlap was between stimulant use during pregnancy and Ritalin use during pregnancy (0.63). Because this was the only large overlap all variables were utilised in model building, however, in cases where both these variables (i.e. stimulant and Ritalin use during pregnancy) were significant predictors, thought was given as to which provided the stronger contribution to the variance observed.

Fitting of the linear regression model followed two steps. First, all acknowledged co-variate factors were entered into the model and significant ($p < .05$) factors were identified. Second, a forwards and backwards variable elimination was used in order to identify a stable set of variables creating the most parsimonious model.

The results of these analyses are presented in Table 12 through Table 15. Models were first run for methadone exposure alone (i.e. between methadone exposed and controls). These models are presented in Tables 12 and 13. Then run with consideration in regards to exposure related to maternal dose during pregnancy. These models are presented in Tables 14 and 15.

In brief, these models show that even when controlling for confounding variables, methadone exposure during pregnancy remained a significant predictor of a number of infant clinical and neurobehavioural characteristics. Namely, for the clinical characteristics these were birth weight, head circumference (across dose), days in hospital, Finnegan scores and neonatal abstinence treatment and for the neurobehavioural measures: NNNS Attention, NNNS Handling, NNNS Regulation, NNNS Non-optimal Reflexes, NNNS Stress/Abstinence, NNNS Arousal, NNNS Excitability and NNNS Hypertonicity. It should also be noted that in a number of cases (across both clinical and neurobehavioural characteristics) although methadone exposure did not reach significance ($p < .05$) it was close to or nearing significance as opposed to being a complete non-contributor to the model. For example, in the between group models for head circumference (p = .061) and NNNS Habituation (p = .056).

Table 12

Summary of Regression Analysis Considering the Association Between Methadone Exposure During Pregnancy, Covariate Factors and Infant Clinical Characteristics

Clinical Measure	B	SE B	p
Birth Weight (g)			
R^2 = .42, Model *F* (3,89) = 21.83, p < .0001			
Gestational age in weeks	131.98	24.51	<.0001
Marijuana use during pregnancy	-298.75	119.77	.014
Methadone treatment during pregnancy	347.71	105.64	.001
Birth Length (cm)			
R^2 = .28, Model *F* (3,88) = 11.57, p < .0001			
Tobacco use during pregnancy	-4.21	1.28	.001
Stimulant use during pregnancy	-5.92	1.33	<.0001

Methadone treatment during pregnancy	-2.25	1.24	.073
Head Circumference (cm)			
R^2 = .30, Model *F* (3,88) = 12.84, p < .0001			
Gestational Age in weeks	0.32	0.09	<.0001
Benzodiazepine use during pregnancy	-1.24	0.49	.014
Methadone treatment during pregnancy	0.69	0.36	.061
Days in Hospital			
R^2 = .43, Model *F* (2,89) = 33.41, p < .0001			
Stimulant use during pregnancy	8.69	3.12	.006
Methadone treatment during pregnancy	-13.73	3.35	<.0001
Finnegan			
R^2 = .88, Model *F* (2,88) = 319.91, p < .0001			
Opiate use during pregnancy	-1.60	0.77	.039
Methadone treatment during pregnancy	-13.91	0.59	<.0001
NAS Treatment			
R^2 = .74, Model *F* (1,91) = 258.32, p < .0001			
Methadone treatment during pregnancy	-0.86	0.05	<.0001

Table 13

Summary of Regression Analysis Considering the Association Between Methadone Exposure During Pregnancy, Covariate Factors and Infant Neurobehavioural Characteristics

Neurobehavioural Measure	B	SE B	p
NNNS Habituation			
R^2 = .33, Model *F* (2,41) = 9.87, p < .0001			
Benzodiazepine use during pregnancy	-1.88	0.66	.007
Methadone treatment during pregnancy	1.08	0.55	.056
NNNS Attention			
R^2 = .12, Model *F* (1,69) = 9.43, p = .003			
Methadone treatment during pregnancy	1.01	0.33	.003
NNNS Handling			

R^2 = .13, Model *F* (2,78) = 5.97, p = .004			
Maternal psychological health	0.07	0.03	.011
Methadone treatment during pregnancy	-0.18	0.06	.005
NNNS Quality of Movement			
R^2 = .33, Model *F* (3,82) = 13.55, p < .0001			
Tobacco use during pregnancy	-0.65	0.26	.014
Maternal physical health	-0.37	0.10	<.0001
Methadone treatment during pregnancy	0.03	0.28	.926
NNNS Regulation			
R^2 = .40, Model *F* (3,83) = 18.78, p < .0001			
Gestational age in weeks	0.13	0.04	.003
Ritalin during pregnancy	-1.13	0.28	<.0001
Methadone treatment during pregnancy	0.73	1.65	<.0001
NNNS Non-optimal Reflexes			
R^2 = .11, Model *F* (1,88) = 10.51, p = .002			
Methadone treatment during pregnancy	-1.46	0.45	.002
NNNS Stress/Abstinence			
R^2 = .38, Model *F* (4,85) = 13.24, p < .0001			
Gestational age in weeks	-0.01	<0.00	.029
Ritalin use during pregnancy	0.06	0.03	.034
Maternal physical health	0.02	0.01	.008
Methadone treatment during pregnancy	-0.05	0.02	.007
NNNS Arousal			
R^2 = .13, Model *F* (1,85) = 12.87, p = .001			
Methadone treatment during pregnancy	-0.55	0.15	.001
NNNS Excitability			
R^2 = .27, Model *F* (3,86) = 9.87, p < .0001			
Gestational age in weeks	-0.31	0.12	.014
Maternal physical health	0.66	0.26	.014
Methadone treatment during pregnancy	-1.16	0.58	.047
NNNS Hypertonicity			
R^2 = .17, Model *F* (2,85) = 8.62, p < .0001			

Ritalin use during pregnancy	-0.38	0.14	.017
Methadone treatment during pregnancy	0.58	0.24	.009

Table 14

Summary of Regression Analysis Considering the Association Between Methadone Exposure in Regards to Maternal Dose During Pregnancy, Covariate Factors and Infant Clinical Characteristics

Clinical Measure	B	SE B	p
Birth Weight (g)			
R^2 = .45, Model *F* (3,89) = 23.95, p < .0001			
Gestational age in weeks	125.82	24.16	<.0001
Marijuana use during pregnancy	-310.47	113.52	.008
Methadone treatment during pregnancy	-233.87	60.49	<.0001
Birth Length (cm)			
R^2 = .26, Model *F* (3,88) = 10.10, p < .0001			
Tobacco use during pregnancy	-2.68	1.16	.024
Stimulant use during pregnancy	-5.47	1.35	<.0001
Methadone treatment during pregnancy	0.07	0.69	.915
Head Circumference (cm)			
R^2 = .32, Model *F* (3,88) = 13.70, p < .0001			
Gestational Age in weeks	0.31	0.09	.001
Stimulant use during pregnancy	-1.26	0.51	.016
Methadone treatment during pregnancy	-0.60	0.20	.004
Days in Hospital			
R^2 = .44, Model *F* (2,89) = 34.93, p < .0001			
Stimulant use during pregnancy	9.50	3.04	.002
Methadone treatment during pregnancy	8.36	1.24	<.0001
Finnegan			
R^2 = .79, Model *F* (2,88) = 166.56, p < .0001			
Tobacco use during pregnancy	3.82	0.91	<.0001
Methadone treatment during pregnancy	6.23	0.52	<.0001
NAS Treatment			

R^2 = .74, Model *F* (3,89) = 85.59, p < .0001			
Tobacco use during pregnancy	0.18	0.07	.014
Ritalin use during pregnancy	0.25	0.09	.008
Methadone treatment during pregnancy	0.43	0.04	<.0001

Table 15

Summary of Regression Analysis Considering the Association Between Methadone Exposure in Regards to Maternal Dose During Pregnancy, Covariate Factors and Infant Neurobehavioural Characteristics.

Neurobehavioural Measure	B	SE B	p
NNNS Habituation			
R^2 = .30, Model *F* (2,41) = 8.74, p = .001			
Benzodiazepine use during pregnancy	-1.92	0.70	.009
Methadone treatment during pregnancy	-0.48	0.32	.145
NNNS Attention			
R^2 = .16, Model *F* (2,68) = 6.60, p = .002			
Ritalin use during pregnancy	-1.15	0.52	.030
Methadone treatment during pregnancy	-0.52	0.21	.013
NNNS Handling			
R^2 = .11, Model *F* (2,78) = 4.82, p = .011			
Maternal psychological health	0.06	0.03	.017
Methadone treatment during pregnancy	0.09	0.04	.016
NNNS Quality of Movement			
R^2 = .34, Model *F* (3,82) = 13.98, p < .0001			
Tobacco use during pregnancy	-0.55	0.23	.021
Maternal physical health	-0.37	0.10	.001
Methadone treatment during pregnancy	-0.14	0.15	.353
NNNS Regulation			
R^2 = .39, Model *F* (3,83) = 17.45, p < .0001			
Gestational age in weeks	0.12	0.04	.007
Ritalin during pregnancy	-1.30	0.28	<.0001

Methadone treatment during pregnancy	-0.39	0.10	<.0001
NNNS Non-optimal Reflexes			
R^2 = .17, Model *F* (1,88) = 18.22, p < .0001			
Methadone treatment during pregnancy	1.01	0.26	<.0001
NNNS Stress/Abstinence			
R^2 = .37, Model *F* (4,85) = 12.32, p < .0001			
Gestational age in weeks	-0.01	<0.00	.041
Ritalin use during pregnancy	0.07	0.03	.013
Maternal physical health	0.02	0.01	.006
Methadone treatment during pregnancy	0.03	0.01	.027
NNNS Arousal			
R^2 = .23, Model *F* (3,83) = 8.31, p < .0001			
Gestational age in weeks	-0.09	0.04	.020
Ritalin use during pregnancy	0.51	0.24	.037
Methadone treatment during pregnancy	0.28	0.09	.002
NNNS Excitability			
R^2 = .28, Model *F* (3,86) = 11.19, p < .0001			
Gestational age in weeks	-0.28	0.12	.024
Maternal physical health	0.59	0.26	.026
Methadone treatment during pregnancy	0.84	0.34	.016
NNNS Hypertonicity			
R^2 = .22, Model *F* (2,85) = 12.05, p < .0001			
Ritalin use during pregnancy	0.63	0.16	.006
Methadone treatment during pregnancy	0.29	0.09	<.0001

In order to help understand what these models represent in terms definable differences in infant characteristics adjusted means were calculated using the models constructed. Table 16 to Table 19 display these adjusted means. These means provide an illustration of what would be expected if all infants had been exposed to similar levels of the confounding variables. That is, they offer a representation of the differences that would be expected from the influence of methadone exposure alone (as if other factors known to influence these measures were held constant).

Mean birth weight ($p = .001$), Finnegan scores ($p < .0001$) and days in hospital ($p < .0001$) remained significantly different between the two groups. Differences between the head circumferences of the two groups was no longer significantly different ($p = .061$) and as was mean difference in birth length ($p = .073$). The majority of NNNS summary measures remained significantly different between the two groups ($p < .05$) with the exceptions being Quality of Movement ($p = .926$) and Habituation ($p = .056$).

When means were calculated across all three dose measures it becomes easier to see what exposure to methadone might mean for these infants. On the whole similar results were obtained but with differences becoming more clearly pronounced. Of note is the clinical characteristic of head circumference. When the model is considered across dose rather than solely between exposure and non-exposure a significant difference between groups re-appears ($p = .004$). Among the NNNS summary scores again a similar pattern of results occurred as with the between group findings with clear linear trends apparent across the majority of the means. Only the NNNS summary scores of Quality of Movement ($p = .353$) and Habituation ($p = .145$) returned values that suggested there were no differences between the groups.

Table 16

Means of Infant Clinical Characteristics Adjusted for Confounding Variables

Clinical Measure	ME (n = 51)	Control (n = 42)	p
M Birth Weight (g)	3,039.22	3,386.94	.001
M Birth Length (cm)	51.74	49.49	.073
M Head Circ. (cm)	33.83	34.52	.061
M Days in Hospital	17.47	3.73	<.0001
M > Finnegan	13.62	N/A	<.0001

Table 17

Means of Infant Neurobehavioural Scores on NNNS Assessment Adjusted for Confounding Variables

Neurobehavioural Measure	ME (n = 51)	Control (n = 42)	p
M Habituation	6.21	7.29	.056
M Attention	5.88	6.90	.003
M Handling	0.32	0.14	.005
M Quality of Movement	4.36	4.38	.926
M Regulation	5.42	6.15	<.0001
M Non-Optimal Reflexes	4.32	2.86	.002
M Stress/Abstinence	0.17	0.12	.007
M Arousal	4.39	3.84	.001
M Excitability	3.79	2.63	.047
M Hypertonicity	0.52	0.14	.009

Table 18

Means of Infant Clinical Characteristics Adjusted for Confounding Variables Across Maternal Dose Groupings

Clinical Measure	No Dose (n = 42)	Low Dose (n = 26)	High Dose (n = 25)	p
M Birth Weight (g)	3,386.82	3,152.95	2919.07	<.0001
M Birth Length (cm)	50.68	50.75	50.82	.915
M Head Circ. (cm)	34.64	34.04	33.43	.004
M Days in Hospital	4.42	12.79	21.15	<.0001
M > Finnegan	N/A	8.52	14.76	<.0001

Table 19

Means of Infant Neurobehavioural Scores on NNNS Assessment Adjusted for Confounding Variables Across Maternal Dose Groupings

Neurobehavioural Measure	No Dose (n = 42)	Low Dose (n = 26)	High Dose (n = 25)	p
M Habituation	7.10	6.62	6.12	.145
M Attention	6.82	6.30	5.78	.013
M Handling	0.17	0.26	0.36	.015
M Quality of Movement	4.48	4.34	4.20	.353
M Regulation	6.08	5.69	5.29	<.0001
M Non-Optimal Reflexes	2.75	3.84	4.93	<.0001
M Stress/Abstinence	0.12	0.15	0.17	.027
M Arousal	3.90	4.18	4.46	.002
M Excitability	2.56	3.40	4.24	.016
M Hypertonicity	0.11	0.40	0.70	<.0001

Discussion

4.1 Summary of Findings of the Current Research

The current study examined five hypotheses in relation to infant clinical and neurobehavioural outcomes at term for infants exposed prenatally to methadone.

Brief Summary of Findings Relating to Hypothesis One

Methadone exposed infants were significantly lighter, had smaller head circumferences and spent longer in hospital than the non-exposed infants.

Brief Summary of Findings Relating to Hypothesis Two

Methadone exposed infants had significantly different profiles across the neurobehavioural measures of NNNS Regulation, NNNS Attention, NNNS Excitability, NNNS Arousal, NNNS Handling and NNNS Habituation. Descriptively, this manifested itself as a more volatile infant, who was easily aroused but difficult to maintain in a happy attentive alert state. Instead, the infant was often quick to cry and difficult to soothe. Frequently, these infants showed less motor maturity and displayed numerous signs that they were going through withdrawal.

Brief Summary of Findings Relating to Hypothesis Three

Acoustically these infants also often sounded quite different. Although statistically there was no difference in the pitch of the cries of the two groups, the infants exposed to methadone showed much greater variability in the cycle-to-cycle microfluctuations of cry. This can be heard in the harsh or rough sounding quality of these infants' cries.

Brief Summary of Findings Relating to Hypothesis Four

When the data were analysed on the basis of maternal dose, infants in the group exposed to higher maternal doses during pregnancy fared less well than those exposed to lower maternal doses.

Brief Summary of Findings Relating to Hypothesis Five

Careful consideration of a large number of confounding variables showed that even after controlling for these variables prenatal exposure to methadone made a significant independent contribution to increasing both clinical and neurobehavioural risk.

4.2 Detailed Consideration of the Current Study Findings Including Relevance and Links to Previous Research

4.2.1 Clinical Outcomes Associated with Prenatal Methadone Exposure when Measured at Birth

The majority of previous studies that have examined the effect at birth of prenatal exposure to methadone have taken measures of infants' clinical outcomes. This study made clinical findings similar to those reported in previous studies. Where there were differences, findings from the current study appeared less unfavourable than those of previous research.

Consistent with much of the earlier research the current study found infants in the methadone exposed group had a mean gestational age just under 39 weeks which reflected a slightly shorter gestation when compared to the non-exposed comparison infants. As with previous studies this was not a statistically significant finding.

The mean birth weight of the methadone exposed infants in the current study was slightly higher (approx 2,900 gm) than the means cited in previous literature (approx 2,700 gm). Despite this discrepancy there was still a statistically significant difference between the infants exposed to methadone and the non-methadone exposed infants in the current study who had a mean birth weight (approximately 3,400 gm), consistent with the national average.

Similar to previous studies, the current study found that infants exposed to methadone in utero had smaller head circumferences than their non-exposed comparisons. However, as with birth weight, the mean head circumference measurement of the current study (33.6 cm) was slightly closer to that of the non-methadone exposed infants (34.8 cm) than the mean of head circumferences reported in previous studies (32.17 cm) (Chasnoff et al., 1984; Choo et al., 2004; Hagopian et al., 1996; Lester et al., 2002).

The current study examined infant birth length, a clinical measurement not considered in the majority of previous studies. Although differences in birth length between the two groups did not reach significance there may have been a trend towards smaller infants in the methadone exposed group.

When considered in context of all confounding variables, the combination of birth measurements in the current study suggest that methadone exposed infants are at increased risk of being born symmetrically smaller than their non-methadone exposed counterparts. Previous research on non-drug exposed infants has found that symmetrically smaller infants are at an increased risk of developing social, behavioural, and learning difficulties (Davis, 2003; Hack & Fanaroff, 2000; Taylor et al., 2000). It is the finding of smaller head circumference (that differentiates asymmetrically from symmetrically smaller infants) that is especially worrying. This is because head circumference has been directly correlated with IQ (Rushton & Ankney, 1996). Furthermore, there has been recent evidence to suggest that restricted brain growth in utero may have long term effects that are not ameliorated by postnatal growth catch-up (Frisk, Amsel, & Whyte, cited in Wouldes & Woodward, submitted)

After confounding variables were controlled for, the difference in birth weights became smaller but remained statistically significant, while the differences in head circumference measurements were no longer significant but the possibility of a trend remained. After confounding variables were controlled for, birth length was longer for those in the methadone exposed group than for those in the non-methadone exposed group. These findings suggest that confounding variables considerably attenuate the effects typically associated with prenatal methadone exposure in regards to the birth measurements of the

newborn. For birth length, the factors of maternal tobacco and stimulant use during pregnancy appeared to play a stronger role. For head circumference, gestational age and maternal benzodiazepine use during pregnancy were important. These findings are in contrast to those of Wouldes and Woodward (submitted), who continued to find strong support for the effects of prenatal methadone exposure across all birth measurements after controlling for maternal factors. It is difficult to explain the finding of longer birth length, in the methadone exposed infant either clinically or statistically.

The mean for total days spent in hospital was not dissimilar from what has been previously reported. Although compared cautiously, due to the possibility of regulatory differences, the current finding of approximately 18 days is close to both older (mean of 15 days found by Blinick et al, 1973) and later studies (mean of 14 days found by McCarthy et al., 2005), and definitely within the range of what has been previously reported. Unlike the birth dimensions, adjusted estimates of duration of infant hospital stay were similar to those of Wouldes and Woodward (submitted) after controlling for confounding variables.

The current study also reported findings within, but at the upper end of the previously cited ranges for NAS (which are between 48 and 95%). Unsurprisingly, infants exposed to methadone in utero displayed greater signs of stress and withdrawal in comparison to their control counterparts. This fits with the comments made by Rosen and Johnson (1993) that it is typical to continue to find traces of opiates in infant urine during the first three weeks of life. This indicates that these infants are likely to still be going through withdrawal. In accordance with this, almost ninety percent of infants in the current methadone exposed group required treatment for abstinence symptomatology. It is likely that this accounts for a substantial part of the reason that the average hospital stay for methadone exposed infants was approximately six times longer than that of those in the control group.

Similarly, as is the case with most of the previous research, there were no differences in APGAR scores associated with prenatal methadone exposure. This consistent finding would indicate that APGAR scores are not a reliable means of differentiating infants exposed to methadone in utero. It also implies that for the most part, these infants are not in immediate need of medical attention as a result of prenatal methadone exposure.

4.2.2 Neurobehavioural Outcomes Associated with Prenatal Methadone Exposure When Measured at Birth

4.2.2.1 Infant NNNS Assessment Outcomes

Information gleaned from the NNNS assessment conducted around two weeks of age revealed similar behavioural profiles to earlier research (Bada et al., 2002; Chasnoff et al., 1984; Lester et al., 2002). The majority of NNNS summary themes showed a significant difference between the two groups. Infants prenatally exposed to methadone were significantly less well regulated, less attentive, more aroused, and more excitable than their non-exposed counterparts. In addition they were more hypertonic, showed less motor maturity, required more assessor assistance to calm and displayed more stress and abstinence symptomatology.

The current study is unique, to the author's knowledge, in the extent to which it examined the influence of confounding variables on neurobehavioural outcomes typically associated with prenatal methadone exposure. Even after control for confounding variables there were numerous significant differences between the NNNS profiles of the two groups. Most notable of these was the difference in infants' NNNS Regulation summary scores. Regulation is the most global of the NNNS summary scores and in essence reflects a combination of a number of the other summary scores. More definitively, it provides an indication of the infant's physiological and attentional activation, the infant's ability to control its own state of arousal in response to the external environment, and the external support required by the infant. The current results suggest that even after factoring out a large number of other variables that might influence the newborn's regulation capability, exposure to maternally ingested methadone while in utero plays a significant role in the newborn's ability to develop this skill. Learning to self regulate is an essential building block upon which a large number of later skills rely. Therefore, problems or delay in the area of self regulatory abilities may impact on routine development (Schuetze & Eiden, 2006).

The NNNS summary scores of Attention, Arousal, and Handling, and, to a lesser extent, Excitability were also highly significantly different between the two groups, even after controlling for confounding variables. These reflect an infant less able to attend, quicker to cry and requiring more external support. The NNNS Attention and Arousal findings can be regarded as consistent with the orientation items of the NBAS. The findings of the current study are therefore in concurrence with those of Chasnoff et al. (1986), who found significant differences in orientation, between 51 infants exposed to methadone in utero and 27 non-methadone exposed comparison infants. At two weeks old it is difficult to say whether this profile reflects a temperament trait or whether it is a transient observation. Research on a large sample of 394 infants by Sheinkopf et al. (2006) found some evidence of temperament stability over the first four months of life in cocaine exposed infants assessed using the NNNS measure. These researchers cautioned that there is likely to be "only a modest level of stability in early infant behaviour" (p. 34). Whichever may be the case, the combination of these characteristics presents the reality of a newborn that is more easily upset (NNNS Arousal), less able to soothe itself (NNNS Regulation), has difficulty attending (NNNS Attention) and requires greater carer input to soothe (NNNS Handling).

Added to this, the methadone exposed infant is more likely to have increased muscle tone (NNNS Hypertonicity) and display NNNS Non-optimal reflexes. The later are both physiological as well as behavioural markers. Not only can they be used to help identify a vulnerable infant but also they imply further physiological difficulties that the infant must overcome in his or her fragile state. Another of the physiological summary themes, NNNS Quality of Movement, no longer remained a significant differentiating characteristic between the two groups when the role of confounding variables was considered, notably maternal tobacco use and maternal physical health. This suggests that other factors may be more responsible for any difference observed in these infants in regards to motor control such as smoothness of movements.

4.2.2.2 Infant Cry Analysis Outcomes

The mean F_0 (fundamental frequency) of both the methadone exposed infants and the non-methadone exposed comparison infants in the current study was approximately 500 Hertz.

This measurement falls within the range (425-600 Hz) expected of a healthy newborn child (Ostwald and Peltzman, 1974) and is similar to the F_0 reported on relatively large sample sizes (n = 172) in more recent literature (Michelsson et al., 2002). According to a review of the literature, in which differentiation of different cry types are discussed, a F_0 of around 500 Hz is likely to represent good CNS arousal (Soltis, 2004)

The finding of a similar F_0 for both groups was contrary to what was hypothesized. Based on findings of previous research analysing cry characteristics of infants with CNS insults it was anticipated that the F_0 of the methadone exposed group would be higher than that of the non-methadone exposed group. Two possibilities are offered in regards to the current finding. First, in concurrence with the study conducted by Huntington et al., (1990), who also failed to find a difference in $F_{0,}$ the lack of finding may be a result of small sample size. Second, the finding may be a logical extension of the physiological similarities between the two groups. That is, there was no significant difference between the two groups in regards to infant length. Logically, this birth measurement provides the best predictor of average larynx size. Specifically this is likely to indicate that the two groups had similar sized vocal folds and therefore produced the same $F_{0.}$ These two possibilities are not mutually exclusive. That is to say, if a larger sample size was to provide evidence of a difference in body length it may also reveal a difference in $F_{0.}$

The mean length of cry utterance in the current study was approximately 1.4 seconds and did not differ significantly between the two groups. This is similar to the mean reported in Michelsson et al., (2002) but slightly longer than a number of other means reported which are closer to one second (Soltis, 2004). Again, the lack of difference between the two groups could be a reflection of small sample size. However, given the definition used in the current study to qualify a cry utterance (i.e. over one second duration), it is also possible that the lack of difference in utterance duration between the two groups is an artefact of the definition used. A number of infants' cries from both groups were excluded for analysis because they did not reach the one second cut off criteria (evidence of this can be seen in the cry wave forms attached in Appendix 6). It may be warranted to investigate further the number of cry utterances in both groups omitted for definitional reasons.

Although the two groups did not differ in regard to mean F_0 or utterance duration, the finer-grained analysis of F_0 jitter calculations identified clear group differences. This finding was consistent with the hypothesis that the methadone exposed infants' F_0 would display higher rates of jitter than their control counterparts. Given that there were no significant differences between the two groups in regards to age at testing, mean F_0 of the two groups or the types of cries elicited, this is likely to be a valid difference. This suggests that the CNS abnormalities affecting laryngeal behaviour are only apparent in the short term, and that these short term abnormalities are not revealed when measuring average $F_{0.}$ This is probably to be because jitter is a reflection of the microfluctuations of the system. These represent instability of neural control as opposed to elementary differences being observed via cry characteristics such as F_0. In many respects this can be understood as a parallel to NNNS Regulation in that jitter can be understood as poor regulation of the infant's vocal system. This hypothesis fits with the suggestion posited by Grauel, Hock and Rothganger (1990) that jitter is a more sensitive measure than either F_0 or utterance duration. However, as has been mentioned in previous jitter literature, though the sensitivity of jitter measurement may be higher than other cry characteristics, it has low specificity. The differences observed across the jitter measures in the current study may reflect CNS abnormalities related to factors other than prenatal methadone exposure.

4.2.3 Infant Outcomes in Relation to Maternal Methadone Dose During Pregnancy When Measured at Birth.

The current study adds weight to those studies that report that maternal methadone dose does matter. Examination of between group differences found consistent evidence of a negative linear relationship between maternal dose and infant outcomes. That is, the higher the maternal dose, the less favourable the infant outcome. This was true across all significant between group clinical measures and in all but NNNS Handling of the neurobehavioural measures. After controlling for the confounding variables of maternal drug use, maternal health and maternal nutrition, strong dose trends were still apparent. Birth length, NNNS Habituation and NNNS Quality of movement were the only measurements that did not reflect dose trends.

Some measures of outcome showed stronger relationships to maternal methadone dose than other measures. For example, within the neurobehavioural outcomes, the areas of NNNS Regulation, NNNS Non-optimal reflexes, NNNS Arousal and NNNS Hypertonicity appear to be more closely linked to maternal dose than the areas of NNNS Attention, NNNS Handling and counter-intuitively, NNNS Stress/Abstinence. Two possibilities are postulated to account for this. First, it is logical to consider that there are certain areas of the developing infant CNS that are more susceptible to methadone exposure than other areas. It may be the case that these are areas of the brain affected by the neurobehavioural outcomes that show the strongest dose response relationship. Alternatively, it may be that the associations between maternal methadone dose and certain neurobehavioural outcomes are moderated by the role of confounding variables. This suggestion has been raised, either explicitly or more tentatively, by several previous authors in consideration of clinical outcomes (Berghella et al., 2003; Choo et al., 2004; Lester et al., 2002). A variety of confounding variables that may play a moderating role have been suggested including maternal tobacco use, maternal benzodiazepine use and maternal alcohol consumption during pregnancy

The outcome of infant head circumference is worth noting in more detail with reference to maternal methadone dose. Initial between group analyses, of methadone exposed and non-methadone exposed infants, including dose related comparisons, demonstrated that those infants exposed to higher maternal doses had significantly smaller head circumferences. However, later analysis of methadone exposed and non-methadone exposed infants that included consideration of confounding variables attenuated these earlier findings to the point of negating significance. When examined across dose whilst giving consideration to confounding variables, significant returned.

In summary, these findings suggest that infant head circumference is affected by prenatal methadone exposure and that higher levels of methadone exposure negatively influence head circumference. On the other hand, the findings also suggest that infant head circumference is a measure perhaps more closely linked to the confounding variables associated with maternal methadone dose than methadone itself. The current finding is in contrast to those of Hagopian et al., (1996) who found higher maternal methadone dose to

be associated with increased head circumference. They acknowledged that this finding may have been mediated by weight change during pregnancy. All maternal doses in the Hagopian et al., (1996) study were under 60 mg/day. This may relate to the finding above i.e. that infant head circumference is closely linked to confounding variables. In the case of the current discrepancy, it may be that dose effects on infant head circumference are mediated to an extent by maternal weight gain during pregnancy but become evident at higher doses.

4.3 The at Risk Infant in Relation to Environmental Factors

The findings of the current study also raise concerns about the non-optimal family environments into which many of these children are born. As discussed in the methodology, the mothers of these children are more likely to be less well educated, come from a lower socio-economic bracket, be involved in less committed relationships and be coping with higher rates of psychosocial difficulties, including mental health and physical health issues. This combination of factors will generally be associated with reduced access to support and other resources. Bearing in mind that women on the methadone programme are (for the most part) doing their best for their children and trying as hard as any mother would to provide the best environment possible for her child, the reality is that they continue to cope with the consequences of drug addiction, and a large minority are likely to be using illicit drugs. Even without the addition of an unsettled newborn this combination of factors implies higher rates of maternal stress. Previous research has found that higher rates of maternal stress are related to poorer behavioural outcomes during childhood (Goldberg et al., 1997, cited in Sheinkopf et al., 2006). These infants are born into a context that already poses high risk to them.

The combination of an at risk infant in a high risk environment creates the potential for problems in mother infant attachment. Recent research on both drug exposed and non-exposed infants has found that regardless of exposure status parental stress influences parents' perceptions of their infant's temperament with higher levels of parental stress suggesting inflated parental perceptions of difficult infant temperament (Sheinkopf et al., 2006). Research on parental perception of infant cry has found that infant cries with rates

of higher dysphonation and fundamental frequency variation are perceived as more distressing, arousing and grating (Protopapas & Emis, 1997, cited in LaGasse et al., 2005). It has been postulated from an evolutionary perspective that acoustically difficult sounding cries may be more likely to trigger abuse or abuse fantasies in parents (Soltis, 2004). It is logical to consider the possibility that the attachment bond between a mother and her at risk child may be negatively affected by distorted parental perceptions. The importance of the early months of life informing the primary attachment bond (Bowlby, 1979) and the influence of this attachment bond on later attachments, personality development and vulnerability to adverse experiences (Bowlby, 1982) make this is an important consideration.

4.4 Implications of the Current Findings

The current study contributes to knowledge on substance abuse, paediatric psychology, neurobehavioural teratology, and neonatal paediatric research. The results obtained are particularly relevant to the Canterbury region of New Zealand, but they may be generalisable to pregnant women enrolled in methadone maintenance programmes elsewhere. The study provides information that can be used by health professionals working with newborns exposed to methadone in utero and may be useful for mothers of these infants. For example, it is important to reiterate that APGAR scores in no way indicated the vulnerabilities of these infants or indeed even differentiated them from their non-exposed counterparts. Another example concerns the findings of this study that maternal methadone doses over 60 mg/day during pregnancy may have a greater adverse effect on the developing foetus than doses lower than 60 mg/day. Although there is still controversy around such findings, pregnant women on methadone should at least be made aware of this possibility and how it may manifest itself in the newborn. Health professionals working with the newborn should bear this potential in mind when infants exposed to higher dose levels are born. On the other hand, this is not an argument for enforcing lower levels of methadone on women during pregnancy as that might increase the likelihood of withdrawal-related conditions in utero or heighten the likelihood of additional illicit drug use in order to self manage withdrawal. Both these eventualities are known to have detrimental effects on the developing foetus (Finnegan, 1991).

Previous sections of this discussion have highlighted potential risk factors pertaining to the child exposed in utero to methadone, environmental factors, and interactional effects. Some of these risk factors, in particular those pertaining to the child, are often subtle. Although this study has found evidence of differences, significant both clinically and statistically, between methadone exposed and non-methadone exposed infants, the small size of the differences and the comparatively large influence of confounding variables mean that the neurobehavioural measures used are not sensitive enough on their own to be considered clear predictors of these exposed infants' developmental outcomes. However, these particular neurobehavioural measures appear to have strong enough specificity to highlight that these are at risk infants who display a particular neurobehavioural profile in comparison to non-methadone exposed infants. Together the measures used go some way to provide a key to understanding the subtle behavioural differences that are likely to be exhibited by infants prenatally exposed to methadone, and they provide clues to the potential vulnerabilities consequent upon these differences.

A further consideration is that the vulnerabilities of the newborn may not reflect the entire picture. Information from this study adds to the evidence from previous research that prenatal exposure to methadone affects the CNS of the growing infant. Difficulties may not materialize until later years, such as early school years or later teenage development. For example, it is known that one of the areas of the brain most sensitive to insult is the prefrontal cortex, an area responsible for higher level executive functioning. This area of the brain is one of the last to develop, yet it is one responsible for a number of important adult skills such as judgment and planning. Adults with drug addiction have been found to have cognitive deficits in areas that relate to higher level executive functioning (Breiter & Rosen, 1999, cited in Lester et al., 2002). Given the sensitivity of this area to insult, some neurobiological and neurobehavioural aspects of methadone exposure in utero may have a long latency period.

From the author's discussions with pregnant women on the methadone programme revealed that many of them already feel very guilty about the effect their drug use may have had on their child in utero. This has implications for professionals working with these

families. Removal of locus of control and social ostracism have both been reported to increase stress (Powis, Gossop, Bury, Payne, & Griffiths, 2000; Skinner, 1996) Therefore, recommendations to reduce the level of maternal stress and better the environment in which the child will be raised include empowerment and support of these women.

With increasing knowledge there is more hope that appropriate proactive steps can be taken to limit or prevent potential deficits and difficulties.

4.5 Strengths of the Current Study

The strengths of the current study lie in its strong methodological approach and comprehensive consideration of confounding variables. First, the recruitment rate of 82% for women in the methadone maintenance group can be considered high for this population. Other authors have commented on the difficulty of recruitment in this area (Kumpfer, 1998). Frequently these families lead relatively chaotic, stressful lives and may either be difficult to track down or hesitant to consent to being involved with research. This high rate is a reflection of the recruitment effort and rapport built by the research nurse with the women on the methadone maintenance programme. In turn, the level of this rapport is likely to reflect a combination of the consistency of one primary recruiter, the personality of that recruiter and the confidentiality assurance offered by the research group.

Second, the current study utilised a prospective, between groups approach. This differs from many earlier studies that have been retrospective (Berhella et al., 2003; Hagopian et al., 1996; McCarthy et al., 2005) or lacking in control groups (Choo et al., 2004; Kuschel et al., 2004; McCarthy et al., 2005). The use of a prospective approach also means a lesser likelihood of type I errors (a problem associated with retrospective designs).

Third, because the study was conducted in a relatively small city, all women on the methadone maintenance programme had their treatment managed by the same group of people (the CADS Methadone In Pregnancy Clinic) and were required to give birth at the same hospital. This meant all records were comparable and consistent. Dose charts were easier to access, and any questions could be simply directed to the person or people

responsible. The chances of having a woman on the methadone maintenance programme give birth without the study group being contacted were greatly reduced.

Fourth, the study had numerous procedural and measurement strengths. Data were collected by a few trained researchers who underwent inter-rater reliability checks regularly. The measures chosen for use were up-to-date and comprehensive. The neonatal neurobehavioural assessment measure chosen was modern and specifically designed for use with this population. The cry characteristics chosen were well rationalised, and the maternal interview gave an appropriately broad overview of confounding variables. Analyses were thorough and intensive. A large number of confounding variables that have previously been either overlooked or mentioned but not considered were factored into the current analyses.

Finally, it may be said that the results presented in the current study are likely to underestimate rather than overestimate any neurobehavioural effects of methadone exposure in utero on the newborn. This assertion is based on two factors. First, as already mentioned, a number of the more vulnerable infants were not included in the current analyses, specifically, one methadone infant born prior to 33 weeks gestation and three methadone infants who were unable to be assessed using the NNNS examination. Similarly, a qualitative observation of the cry analysis showed that a total of 21 control infants' recordings were required whilst only 12 methadone exposed infants' recordings were required in order to obtain a sub-sample of ten infants' cries from each group that met criteria. Second, the relatively low sample sizes of the current study combined with the subtle differences being examined, would suggest that there is more risk of making a type II error (accepting the null hypothesis when there is in fact a difference) than a type I error (rejecting the null hypothesis when it is correct).

4.6 Limitations of the Current Study.

There are several limitations to this study. Although considerable effort went into voluntary recruitment of the women on the methadone maintenance programme, recruitment rates of women in the control group were comparatively low and hindered by a number of complications. These complications included flaws in the hospital database which caused a large number of the early information mail outs to be sent to women who had already delivered their babies rather than those due for delivery. The use of a hospital database that is updated only intermittently meant that letters were posted out only to women who were due to deliver in the later months (at the end of the database), which provided a smaller number of women from whom randomly to select. It was found that a number of control women had concerns about consenting to participate in a study examining the effects of drugs on newborn infants and/or were concerned about putting their newborn infant through a magnetic resonance imaging (MRI) scan. Along with the typically busy household problems and stress of giving birth and looking after a newborn baby, there are two possible explanations for these concerns that are pertinent to the nature of this study. First, these women may not have understood what being a control entailed and may have been fearful that their own infant might be exposed to methadone in order to participate. Second, given the stigma attached to drug use (especially during pregnancy), control women may not have wanted to be involved with a study that was examining the effects of maternal drug use. To minimise this problem, future studies might make the role of a control mother and infant more explicit in the information mail out or provide incentives (e.g. remuneration or gifts) in order to encourage the women to sign up. Other suggestions include different recruitment techniques, such as advertising at antenatal classes. This has the disadvantage of changing recruitment away from the random approach commonly considered best practice in empirical research. Additionally, an analysis to gain a better understanding of women who do not agree to consent could be undertaken. This might take the form of a follow-up telephone call or the inclusion of a postage paid return envelope with a list of reasons included in the information mail out.

Another problem relevant to any kind of human based research is the labour intensity and associated difficulty of co-ordinating schedules and keeping errors due to differences in time and place of assessments to a minimum. The current study was lucky to have a number of trained and paid researchers involved, for some, such as the research

coordinator, this was their primary employment. This is likely to have minimised this problem. Clarifying in the information mail out the importance of assessment timing and attendance might increase participant motivation.

In issues involving social stigma and safety concerns such as maternal drug use during pregnancy, it is important to consider the validity of self report measures. New Zealand does not require mandatory reporting of maternal drug use, unlike the United States, where the majority of research in this area is undertaken utilising a "Certificate of Confidentiality". As discussed in another New Zealand study (Wouldes and Woodward, submitted), absence of mandatory reporting may have decreased the chances that the women in this study have under-disclosed their drug use. Also, the consistent use of a single interviewer in order to develop rapport and a trusting relationship with the women enrolled in the methadone maintenance programme will have promoted openness. Given that the quantities of both licit and illicit drug use reported in the current study were similar to or higher than those reported in other studies (Lester et al., 2002), it is reasonable to believe that the findings are representative of actual drug use. Additional suggestions for further overcoming this difficulty include the use of meconium testing (which is being undertaken as part of the larger study) or the use of other chemical testing measures, for example, hair analysis.

One of the major methodological shortcomings of the current study was the difficulty maintaining blind testing. Even though precautions were taken to ensure at least one of the NNNS assessors was blind to infant status, this was not always achieved. For the majority of the recruited participants the author of the study (also an NNNS assessor) was heavily involved in control recruitment, including maternal interviews. In addition, the second NNNS assessor was working as the neonatal physiotherapist at the hospital through which all the women were recruited. This meant that at times she was made aware of maternal status via the requirements of her other role. Lack of assessor blinding has been shown in previous research to limit severely the validity of results collected (Schulz & Grimes, 2002). In defence of the current study, three points should be noted. First, the NNNS assessment follows a relatively strict quantitative scoring schedule (a copy of the scoring guide is available online at http://pediatrics.aappublications.org). Second, neither assessor

had knowledge of maternal dose or dose of any infant treatment. Third, randomly selected NNNS assessments of all assessors were cross checked for inter-rater reliability with the original trainer, who was blind to infant status. These three factors are likely to have reduced the amount of bias that the assessors may have unwittingly introduced due to lack of blinding. The issue of blindness needs to be further addressed in future studies.

Another limitation that affects many studies of this kind is the relatively small sample size. Limitations of sample size are particularly evident in the dose-related summary scores of the NNNS assessment, in particular in the NNNS Habituation scores. Approximately half of the infants were not assessed on this measure due to the requirement that the infant be asleep for this to be administered. Sample sizes for the NNNS Habituation measure were 17, 11, and 16 for the non-methadone exposed, lower maternal exposure group and higher maternal exposure groups respectively. Small sample sizes reduce the ability to detect significant between group differences due to a lack of power. This increases the probability of a type II error (accepting the null hypothesis when in actuality a difference does exist). Given the subtle nature of the differences being examined in the current study and the limited sample size, no adjustments were made for multiple comparisons. Lester et al. (2002) noted that this can be considered as a means of maximising sensitivity and minimising type II error. On the other hand, not adjusting for multiple comparisons increases the likelihood of type I error (rejecting the null hypothesis when it is true). A suggestion for future research is to use a larger sample size, perhaps in a multi-site study. Given the time limit imposed on the current research and the reasonable recruitment rates, the sample sizes provided should be considered acceptable.

Despite the strength of the current study in considering a large and varied range of possible confounding variables and their influence on the findings, still more variables could have been considered. Two of the more important variables that have been shown to influence infant outcomes that could have been considered in further detail are maternal socio-economic status (Luo, Wilkins, & Kramer, 2006) and prior pregnancy history (for example, parity). Although both are in some way considered indirectly, for example, nutritional intake has been correlated with socio-economic status (Shi, Lien, Kumar, Dalen, & Holmboe-Ottesen, 2004) and maternal health may be linked to prior pregnancy

history, both could have been considered more directly. Additionally, the analyses of the current study would have benefited from the consideration of interactional effects between confounding variables. This requires a more complex and intensive statistical analysis than was conducted in the current study. The difficulty, however, relates to the sample size required to undertake such a thorough analysis. The examination of the interactional effects of confounding variables would be an area recommended for future research.

4.7 Suggestions and Directions for Future Research

Some avenues of future research have already been suggested within the previous section, which discussed the limitations of the current study. The next section will focus on additional avenues for future research.

As with almost any research in the area of human development, one of the most pressing areas for future research involves longitudinal follow-up, which is planned for the infants in the current study. It is envisaged that the follow-up will utilise comparable and developmentally considered and appropriate measures to reassess the progress of these children as they age. As discussed, many of these children are born into lower socio-economic families and are often subject to pre-existing early risk factors. Follow-up needs to take into consideration the interplay between contextual factors and the effects of early exposure to methadone during pregnancy. Follow-up will also be useful in determining the predictive value of both the NNNS and jitter analysis in regards to the developmental outcome of these infants. Particular areas of interest for follow-up that have stemmed from the current research include the self-regulatory processes of these children and further examination of how these develop. An interesting adjunct would be to examine if these self-regulatory difficulties relate to later childhood difficulties in areas such as attention deficit, attachment, and emotional development. This subsequent research will be instrumental in clarifying what early intervention strategies may be required in future for the offspring of mothers using methadone. Ultimately, follow-up should be conducted on a regular basis through to adulthood or to a point where, after so many years, follow-up can no longer discern the influence of methadone exposure in utero on the developing child.

Another research avenue that would both benefit this population and provide useful knowledge in regards to the sensitivity and specificity of predictive measures would be to undertake a serial assessment study. For example, a combination of the NNNS assessment and cry analyses used in the current study could applied at birth, two weeks, four weeks, and six weeks. This type of research might help differentiate the effects of NAS from the influence of infant temperament. It would also provide a more detailed and comprehensive picture of how these infants' vulnerabilities change over the initial weeks of life when withdrawal is at its most severe. It may also provide insight into resilience patterns associated with factors such as gender. Last, multiple comparisons over a relatively short period of time might offer answers as to the most pervasive difficulties these infants face and how best to identify the infants at the highest risk. Correlations between the neurobehavioural measures could be utilised to examine predictive validity and discriminant analysis could be undertaken to identify the most efficient predictors of infant vulnerability.

Methadone maintenance is used worldwide in the treatment of opiate addiction and therefore requires research across several countries and cultures. To examine the validity and improve the generalisablitiy of this research, it is recommended that future research is undertaken in multiple settings across a variety of cultures. To date, the majority of research in the area has been conducted in the United States, often with high percentages of African American women and their infants living in high density urban areas characterised by poverty (Choo et al., 2004; Hagopian et al., 1996; Householder et al., 1982; Lester et al., 2002)

Given that the results of the current study reflect physiological differences (for example, hypertonicity, non-optimal reflexes, and higher percentages of vocal tract variability) as well as neurological (CNS) differences in infants prenatally exposed to methadone, future research should consider the use of biologically based measures to help establish physiological markers that may provide clues to the vulnerabilities faced by these infants. Suggested areas of research include examining cortisol levels and the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis in these infants. This would have the two-fold advantage of seeking replication of the current findings and allowing more

refined quantification of these findings. Future research should attempt to address the questions: What do these physiological differences mean? Are these infants more biologically susceptible to stressors? Does early prenatal exposure make these infants biologically vulnerable to related substance addictions in later life? How can the risks be minimised? And, perhaps counter-intuitively, are there any advantages to be found for infants exposed prenatally to methadone?

The current research suggests the value of qualitative research in the area. What are the values and beliefs of the parents of these infants? It was observed in the current study that many of the women in the methadone maintenance group felt very guilty about exposing their unborn child to methadone (on the basis of their own addiction). It was considered that a large number of potential control recruits were unclear of what "control" meant. Qualitative research into areas such as these and the dissemination of the findings may go a long way to reducing stereotypes. It could help reduce social stigma attached to treatment for addictions, and it may provide information useful for other disciplines involved in the area such as nurses and developmental therapists. Similarly, qualitative case studies on a number of the dyads in the current study could offer connections to real life examples. Doing such research can provide information about and insight into lifestyles of families affected by methadone and the stresses they face. Frequently these aspects are easily overlooked or dismissed in quantitative research.

Finally, much of the information and many aspects of the methodology from the current study could be utilised in future research in other areas of prenatal teratogen exposure, for example, the rapidly growing area of methamphetamine exposure.

4.8 Concluding Remarks

The current study examined the effects of prenatal exposure to methadone on clinical and neurobehavioural outcomes of infants between 40 and 42 weeks gestation. To a large extent study hypotheses were confirmed, with results in general suggesting that methadone exposed infants tended to fare less well than their non-methadone exposed counterparts across a range of both clinical and neurobehavioural measures. This remained the case

even after controlling for a number of confounding variables. Furthermore, there was evidence to suggest that higher maternal methadone doses were associated with worse outcomes than lower doses. Current trends indicate average methadone maintenance dose while pregnant is rising. They also indicate that the number of women enrolled in methadone maintenance programmes and therefore the number of infants being born prenatally exposed to methadone is also rising. The current findings therefore have increasing social and economic implications.

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Appendix 1: A tabular overview of a number of studies relevant to the area.

Design	Source of ME Group	Comparison Group	Maternal Dose	Infant Age at Assessment	Measures	Clinical Findings	Neuro behavioural Findings	Acoustic Cry Findings	Dose Response	
[1] Rosen & Johnson (1988)	Pro-spective	25 pregnant women from prenatal clinic	1. 42 multidrug users 2. 44 controls	X = 52.mg/day (1st trimester) 49mg/day (2nd trimester)	Birth F/U = 2wks, 2months, 4, 6, 12 months.	• Clinical Data • Brazelton (NBAS) • Withdrawal	M E infants worst. + rates prem, -BW, -HC, +SGA, + withdrawal	lower interaction scores on NBAS	N/A	N/A
[2] Berghella, Lim, Hill, Cherpes, Chennat, &Kaltenbach (2003)	Retro-spective	100 mother /neonate pairs identified from hosp records	None Post hoc multidrug versus only methadone	Divided into low (<80 mg/day, x=82) and high (>80mg/day, x=95) dose groups	Every 8 hrs for first 72 hrs of life	• Neonatal Abstinence Score (NAS)	No comparison avail. XBW = 2,716grms	(67% required treatment for NAS)	N/A	No sig dose relationship to BW, NAS or duration of treatment.

[3] McCarthy, Leamon, Parr & Anania (2005)	Retro-spective	81 mother /neonate pairs enrolled in MM treatment clinic.	None	Divided into low (<100mg/day, x=62) and high (>100mg/day, x=132) dose groups	Birth Hospital stay	• Limited Clinical Data • NAS (Finnegan? Doesn't say) • Treatment factors	No comparison avail. X gestation at delivery = 37 wks. XBW = 2,792grms No major abnormalities	(46% required treatment for NAS)	N/A	No sig dose relationship in regards to clinical findings, treatment for neonatal abstinence or days in hosp.
[4] Chasnoff, Schnoll, Burns & Burns (1984)	Pro-spective	39 mother /neonate pairs enrolled in Addiction Project placed on MM	1. 19 mother/ neonate pairs addicted to multiple drugs 2. 27 mother/ neonate pairs no drug history	X = 14.6mg/day Trimester three (Range = 5-40mg/day)	Birth F/U = 3, 6, 12 and 24months	• Clinical Data • Brazelton (NBAS) • Bayleys for F/U	M E infants worst. Sig -BW, -BL, -HC	Sig diff state control, visual and auditory orientation and motor maturity	N/A	N/A
[5] Sharpe & Kuschel (2003)	Retro-spective	24 MM from hospital database	19 Mother's on Methadone for pain management	X = 60mg/day MM group X = 40mg.day pain management group	Birth Hospital Stay	• Clinical Data • Finnegan • Treatment factors • Adverse Complication	In comparison with Pain Management Infants: - rates prem - BW, -HC, + treatment	None taken	N/A	Possible dose response but unclear and unspecified.

[6] Lester, LeGasse, Siefer, Tronick, Baur, Shankaran, Bada, Wright, Smeriglio, Liu, Finnegan & Maza (2003)	Pro-spective.	4 Urban University Based Research Sites 67 self-reported opiate exposed women	1. 360 self reported cocaine exposed women. 2. 554 comparison infants matched on race, sex and gestational age. (no cocaine or opiates)	Self reported opiate exposure, confirmed by meconium assay	One month	• Limited Clinical data • Auditory Brain Response Procedure	No sig diffs at one month	Not discussed	N/A	"Longer latency to peak V and a longer III-V interpeak latency" (p279)
[7] Lester, LeGasse, Siefer, Tronick, Baur, Shankaran, Bada, Wright, Smeriglio, Liu, Finnegan & Maza (2002)	Pro-spective.	4 Urban University Based Research Sites 91 self-reported opiate exposed women	1. 460 self reported cocaine exposed women. 2. 1,120 comparison infants matched on race, sex and gestational age. (no opiates)	Self reported opiate exposure, confirmed by meconium assay	One month (42-44wks gest age)	• Clinical data • NNNS • Cry Analysis	No sig diffs in gestational age	No adjustment for covariants. Higher orientation scores and more stress abstinence signs. After adjustment for covariates no significant effects	Fewer short utterances and more hyper-phonation (high pitch).	N/A
[8] Blinick, Jezez & Walach (1973)	Pro-spective	105 consecutive pregnancies of women enrolled in MM treatment.	None	80-100mg/day	Birth Hospital stay F/U = Up to 4 yrs	• Limited Clinical Data • Withdrawal • Treatment factors	-BW, 10% depressed APGAR scores, 58% withdrawal signs	(26% required treatment)	N/A	N/A

[9] Choo, Huetis, Schroeder, Shin & Jones (2004)	Pro-spective	38 women recruited from a MM centre (divided into light and heavy smokers)	None	X = 77mg/day	Birth	• Clinical Data • Finnegan (NAS) every 4-12hrs for first 4days of life	No diff in BW or HC across the two groups	Withdrawal symptoms in the high smoking group were more severe, peaked later and lasted longer.	N/A	N/A
[10] Fajemirokun-Odudeyi, Sinha, Tutty, Pairaudeau, Armstrong, Phillips, & Lindow (2005)	Retro-spective	108 women (110 babies) 52 women taking methadone alone 47 women taking heroin (+/- methadone)	None 47 women taking heroin (+/- methadone)	X = 32mg/day (at delivery) for MM only X = 33mg/day (at delivery) for heroin +/- methadone)	Birth Hospital stay	• Clinical data • Treatment factors • NAS (Finnegan? Doesn't say)	No sig diffs in clinical data between two groups.	Methadone only infants shorter neonatal stays, lower maximum NAS scores, lower dosages for treatment of NAS.	N/A	NA (similar methadone doses across the two groups)
[11] Kuschel, Austerberry, Cornwell, Couch & Rowley (2004)	Pro-spective	25 infants 20 born to mothers from the ADAPT service (Akl) 5 via pain management	None	X = 55mg/day (range 15-105)	Birth and 48hrs	• Clinical data • Finnegan (NAS) • Treatment factors	No comparison avail. X gestation at delivery = 38 wks. XBW = 2,995grms	(48% required treatment)	N/A	Measured via umbilical cord blood. No significant relationship between maternal dose and need for treatment.

[12] Lejeune, Simmat-Durand, Gourarier & Aubisson (2005) In Press	Pro-spective	100 women from 35 perinatal centres of public hospitals.	159 women on high-dose buprenophine (HDB)	X = 57mg/day (10-180 methadone) X = 5.4mg/day (0.4-24 HDB)	Birth Hospital stay	• Clinical data • Lipsitz (NAS) • Treatment factors	No sig diffs in clinical data between two groups. MM XGestational age = 38.4 XBW = 2,790grms	Mean age at maximum Lipsitz score higher for infants exposed to MM. (trend)	N/A	N/A
[13] Hagopian, Wolfe, Sokol, Ager, Warddell, &Cepeda (1996)	Retro-spective	172 opiate-addicted women enrolled in MM programme in an urban hospital	None	X = 0.19mg/kg/day (Clinic dose prior to delivery range 10-60mg/day)	Birth Hospital stay	• Clinical data • Neonatal withdrawal (doesn't specify) • Treatment factors	No comparison avail. X gestation at delivery = 38 wks. XBW = 2,659grms	(Percentages for neonatal withdrawal No withdrawal = 2% Mild = 12% Mod = 58% Severe = 30%)	N/A	Increased methadone dose associated with larger head circumference and growth but also more severe withdrawal.

[14] Rosen & Johnson (1985)	Pro-spective	57 women on methadone maintenance (61 infants)	32 comparison infants	X = 42 mg/day	Birth F/U = up to 36months the age 4, 5, 6 and 7 yrs	• Clinical data • Finnegan • Brazelton (NBAS) • Treatment factors	+SGA, -HC,	(75% mod-severe withdrawal) Habituated less well, less responsive to orientation items, less alert, less cuddly, less consolable, increased tone and more tremulousness.		Dose correlated positively with severity of NAS and BW.
[15] Jeremy & Hans (1985)	Pro-spectve	26 mothers (29 infants) recruited via obstetrical clinics.	35 mothers (36 infants) recruited via obstetrical clinics at same hospital.	X = 19.3 mg/day (range 3-40)	Birth 1st week of life 1 month	• Clinical data • Neonatal Behavioural Assessment Scale with Kansas Supplements (NBAS-K)	-BW (sig unspecified) NB. Infants less than 2,500g and less than 38wks gestation removed from analyses.	No pharmacologic al treatment for any of the group. At first test sig differences mainly related to motor functioning: more hypertonic, less motor maturity, more active, more tremulousness, more irritable.	N/A	No sig effects related to dosage

[16] Bada, Bauer, Shankaran, Lester, Wright, Das, Poole, Smeriglio, Finnegan, Maza (2002)	Pro-spective	University Based Research Sites 100 self-reported opiate exposed women	1. 7,442 non exposed infants 2. 717 cocaine exposed infants 3. 92 Cocaine and opiate exposed infants	Self reported opiate exposure, confirmed by meconium assay	Birth First 24-72 hrs (X = 36hrs)	• Clinical data • CNS/ANS signs as described in Finnegan's Neonatal Abstinence Scoring System	No sig diffs in BW and GA for the opiate exposed group in comparison to the non exposed infants. But sig -HC	Opiate only exposed infants showed a number of CNS/ANS signs that were significantly higher than either cocaine or non-exposed groups. Particularly jitteriness/ tremors and irritability	N/A	N/A
[17] Sinha, Ohadike, Carrick, Pairaudeau, Armstrong & Lindow (2001)	Retro-spective	Hull Maternity Hospital (as reported in records via referral letter from GP or antenatal interview)	22 women taking methadone only during third trimester (22 infants)	1. 19 women taking heroin during third trimester (19 infants) 2. 10 women who stopped using opiates during pregnancy (10 infants)	Birth Hospital stay	• Clinical data • Neonatal withdrawal (via a "neonatal abstinence sheet") • Treatment factors	Significances not reported. XBW = 2868 (M), 2754 (H) & 3008 (nil) X gestation at delivery =38.2 (M), 36.5 (H), & 39 (nil)	Methadone exposed infants sign shorter NAS duration and sig shorter stays in NICU when compared with heroin exposed infants	N/A	Higher doses associated with sig longer NAS duration and sig longer stays in NICU.

Key:
- = lower
+ = higher
BW = birth weight
Prem = prematurity
HC = head circumference
SGA = Small for gestational age
MM = Methadone Maintenance
N/A = Not applicable (analysis not undertaken)

Appendix 2: Golub and Corwin's (1985) Physioacoustic Model of Infant Cry (p. 65)

A PHYSIOACOUSTIC MODEL OF THE INFANT CRY

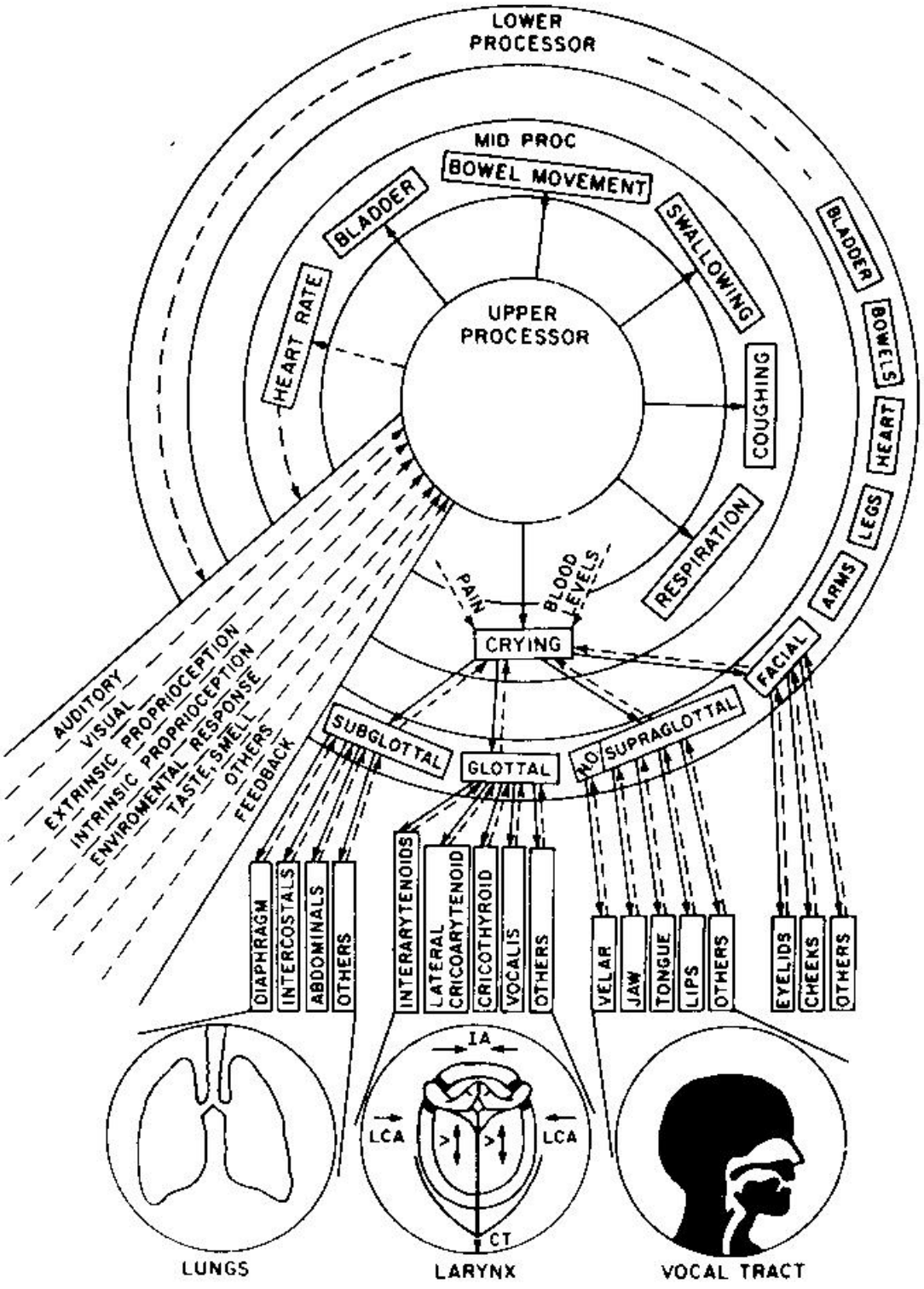
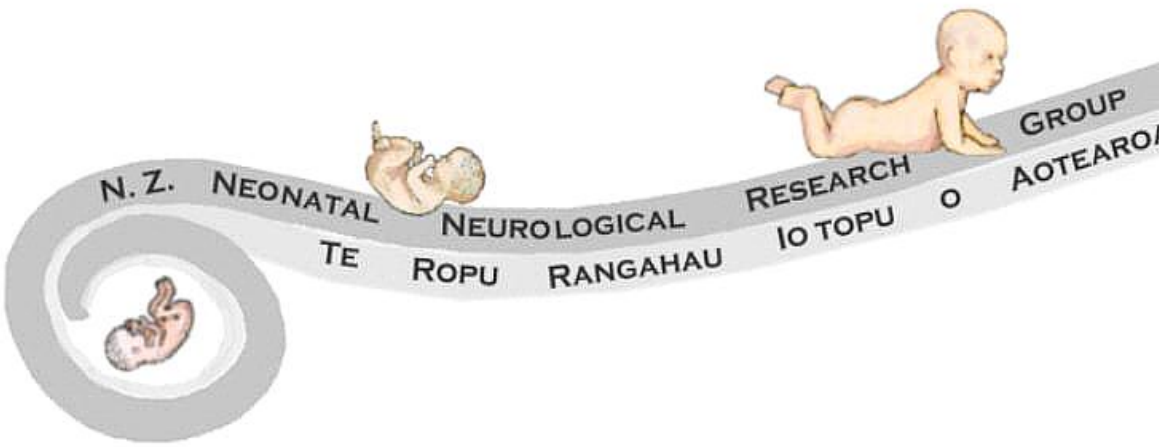


Figure 3. Conceptualization of the organization of the control of the infant cry, showing the proposed upper, middle, and lower processors.

Appendix 3: Recruitment Information Sheet and Consent Form



Woman's Health Division, Department of Paediatrics, Christchurch,
Canterbury Child Development Group, University of Canterbury,
Psychological Medicine, Christchurch School of Medicine, NZ

METHADONE IN PREGNANCY STUDY

INFORMATION SHEET

You are invited to participate with your baby in a study being carried out by Lianne Woodward, a Developmental Psychologist from the University of Canterbury, Carole Spencer, a Research Nurse from Christchurch Women's Hospital, and Jill McKie, a Neonatal Paediatrician from Christchurch Women's Hospital.

WHAT IS THE STUDY?

The purpose of the study is to learn more about the growth and development of babies born to mothers who received methadone during their pregnancy. At present we know that most of these babies develop quite normally, while a small group of babies may develop problems and not do so well. The kinds of difficulties that these children can sometimes experience include health, learning and behaviour problems.

We would like to learn more about what causes some babies to develop problems and to find better ways of detecting babies with early difficulties. This information will help improve the treatment of mothers and their babies in the future.

The study will involve two groups of babies and their mothers. These groups include: a group of babies born to mothers on methadone during their pregnancy and a group of babies born to mothers not on methadone during their pregnancy.

WHAT DOES THE STUDY INVOLVE?

If you agree to take part, we will ask you some background questions about yourself, your pregnancy, and when and where you expect to deliver your baby. Then following the delivery of your baby we will visit you and your baby in hospital. This visit will consist of three parts.

1. The first part will involve a brief interview with you about your pregnancy and how the delivery went. This will take about 30-40 minutes.

2. The second part will consist of a detailed assessment of your baby. This assessment will consist of a detailed physical examination of your baby and an evaluation of your baby's ability to change their behaviour in response to different situations such as being unwrapped or cuddled. We will look for signs that your baby is healthy such as how well s/he can control their behaviour and feelings, communicate their needs by crying, and whether s/he shows any symptoms of withdrawal or neurological distress. This assessment will take about 1/2 hour.

3. In the third part of the study your baby will undergo a magnetic resonance image scan. The scanner will take pictures of your baby's brain using magnetic and radiowaves. No medications or x-rays will be used. Before the scan your baby will be fed in the usual way. He or she will then be laid down in a comfortable pillow in the scanner and monitored over the scan time. The scan will take approximately 1 hour. During the scan we anticipate that your baby will sleep as normal after being fed.

4. Following our assessment of your baby, we will discuss this with you and you will have an opportunity to consider whether you would like your baby's results to be forwarded to your Paediatrician or GP.

BENEFITS

Participation in this study will in no way affect your hospital care. Following our assessment, you will be given a formal report of your baby's assessment and scan results, along with time to discuss the results. If you want, we can also arrange for these results to be sent to your baby's GP or paediatrician.

INCONVENIENCES OR HAZARDS WHICH MIGHT BE EXPECTED

There are no known risks to magnetic resonance imaging. Such scans are routinely done in infants. Most infants will sleep or rest quietly during the study. If your baby wakes or becomes distressed for any reason, the study will be stopped. An additional appointment time will be offered to you if the scan must be stopped. Sedative medications will not be used.

PARTICIPATION

Your participation in this study is entirely voluntary, you do not have to take part if you do not wish. If you agree to take part in the study you are free to withdraw at any time without giving a reason and this will not affect your or your baby's future care. If you have any queries or concerns about your rights as a participant in this study you may wish to contact the Health and Disability Service Consumer Advocate on telephone (03) 377 7501 or 0800 377 766 outside Christchurch.

COMPENSATION

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs ad expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

CONFIDENTIALITY

All information you give us will be treated in the strictest confidence. Your identity will not be revealed in any reports based on the study. No information will ever be released about you or your baby to a third party without your written consent. The study will have a comprehensive security system, with all information you provide being stored anonymously on computer files. Access to these files will be confined to study investigators.

IF YOU WANT TO KNOW MORE

If you want to know more about the study (either now or at a later date) please feel free to contact either:

Names Removed for Privacy Purposes

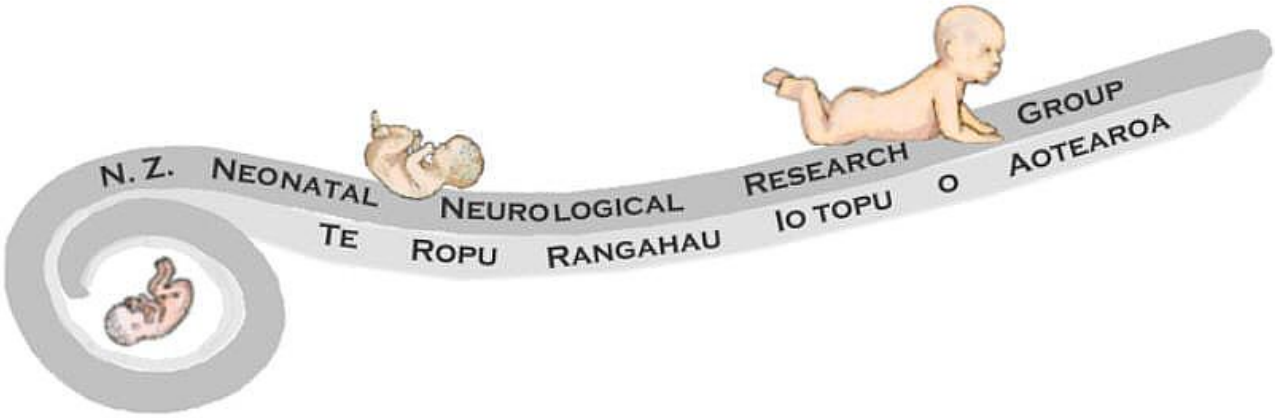
*W*e are committed to treating all our study participants in a fair and ethical manner. This study has received ethical approval from the Canterbury Ethics Committee.

Finally, we would like to thank you for considering assisting us with this research.

Lianne Woodward	Carole Spencer	Jill McKie
Principal Investigator	Research Nurse	Co-Investigator

APPROVED BY THE CANTERBURY ETHICS COMMITTEE

August, 2002



Woman's Health Division, Department of Paediatrics, Christchurch,
NZCanterbury Child Development Group, University of Canterbury, NZ
Psychological Medicine, Christchurch School of Medicine, NZ

CODE NUMBER

Initial Interview Contact Details

Mother's Surname…… Given Names……

Father's Surname……. Given Names……

Child's Name…… Date of Birth……

Address……

……

……

……

……

Phone……

…….

Contact 1:

Name:……Relationship to child…….

Address……

……

……

……Phone……

…….

Contact 2:

Name:……Relationship to child…….

Address……

……

……

……Phone……

…….

Contact 3:

Name:……Relationship to child…….

Address……

……

……

……Phone

…….

Appendix 4: Complete Maternal Interview

METHADONE IN PREGNANCY STUDY

BACKGROUND INTERVIEW

CODE NUMBER	☐☐☐
STATUS CODE	☐
INTERVIEWER	☐
	Day **Month** **Year**
DATE	☐☐ ☐☐ ☐☐

SECTION A. RESPONDENT'S BACKGROUND

A.1 What is your expected date of delivery?

D	D	M	M	Y	Y

Col 18

Mother

A.2 How old were you on your last birthday?

Years

A.3 Which of the following ethnic groups do you belong to or identify with?

	Yes	No
NZ Maori	1	2
NZ European	1	2
Other European (English, Dutch, Scottish, Australian, etc)	1	2
Samoan	1	2
Tongan	1	2
Niuean	1	2
Asian	1	2
Other Specify: _____	1	2

Col 28

A.4 Which of the following best describes your educational qualifications? (circle one)

Left school between 13-16 years	1
Further secondary education	2
Secretarial or trade qualifications	3
Professional qualifications without a degree	4
University degree	5

Other qualifications, specify: _____ | 6 | Col 2

Partner Relations

A.5 Are you currently living with a partner?

Yes, legally married	1
Yes, cohabiting	2
Has partner, not cohabiting	3
No partner	4

A.6 If yes, is he the father of your new baby?

Yes	1	
No	2	
No partner	9	Col 31

IF NO PARTNER ENTER 9s IN A.7 – A.10 AND ASK B.1

A.7 How old is your partner? Years | | |

A.8 Which of the following ethnic groups does your partner belong to or identify?

	Yes	No	NA
NZ Māori	1	2	9
NZ European	1	2	9
Other European (English, Dutch, Australian, etc)	1	2	9
Samoan	1	2	9
Tongan	1	2	9
Niuean	1	2	9

Asian	1	2	9
Other, specify: _____	1	2	9

Col 41

A.9 Which of the following best describes your partner's school/educational qualifications?

Left school between 13-16 years, no qualifications	1
School Certificate (>2 subjects)	2
Further secondary education, eg UE, HSC or Bursary	3
Secretarial or trade qualifications	4
Professional qualifications without a degree	5
University degree	6
Other qualifications, describe: _____	7
Don't know	8
NA (no partner)	9

A.10 How long have you been in this relationship?

Months | | | Col 44

SECTION B. PARENTHOOD

B.1 a) Is this your first pregnancy?

Yes	1
No	2

b) If yes, how many times have you been pregnant before?

Number | | Col 46

IF RESPONDENT HAS HAD OTHER PREGNANCIES, GIVE DETAILS BELOW. IF NO PREVIOUS PREGNANCY ENTER 9's IN RELEVANT ITEMS

PREGNANCY 1: Age became pregnant Years | | |

Outcome of pregnancy	Child kept by respondent	1
	Child adopted	2
	Pregnancy terminated	3
	Miscarriage	4
	Still birth	5
If other, specify: _____	Currently pregnant	6
_____	Other	7
	NA	9 Col 49

PREGNANCY 2: Age became pregnant Years | | |

Outcome of pregnancy	Child kept by respondent	1
	Child adopted	2
	Pregnancy terminated	3
	Miscarriage	4
	Still birth	5
If other, specify: _____	Currently pregnant	6
_____	Other	7
	NA	9 Col 52

PREGNANCY 3: Age became pregnant Years | | |

Outcome of pregnancy	Child kept by respondent	1	
	Child adopted	2	
	Pregnancy terminated	3	
	Miscarriage	4	
	Still birth	5	
If other, specify: _____	Currently pregnant	6	
_____	Other	7	
	NA	9	Col 55

PREGNANCY 4: Age became pregnant Years | | |

Outcome of pregnancy	Child kept by respondent	1	
	Child adopted	2	
	Pregnancy terminated	3	
	Miscarriage	4	
	Still birth	5	
If other, specify: _____	Currently pregnant	6	
_____	Other	7	
	NA	9	Col 58 REC01

IF MORE THAN 4 PREGNANCIES, ENTER DETAILS HERE

Biological Children

B.2 a) Total number of biological children

Number ☐

b) INTERVIEWER: Complete the coding frame for all biological children of the respondent.

Name of Child	DOB			Age (Years)		Gender	Legal Custody	Physical Custody
1 (Eldest)								
2								
3								
4								
5 (Youngest)								

Col 60

Coding: Date of birth: Code day, month, year. NA = 99.
Child's age coded in whole years. NA = 99.
Gender: Female = 1; Male = 2; NA = 9.
Legal custody: Sole = 1; Shared = 2; None (ie, other parent has sole legal custody) = 3; NA = 9.
Physical custody: Sole = 1; Shared = 2; None (ie, no physical contact) = 3; NA = 9.

Record any additional information here: _____

_____

B.3 Do all of these children have the same mother/father?

Yes	1
No	2

Col 61
REC02

If no, please describe: _____

Step or Non-biological Children

B.4 Are you parenting or caring for any children who are not your own?
(Include here all non-biological children)

Number ☐

B.5 Can you tell me the names and ages of each of these children? Complete coding frame for non-biological children)

Name of Child	DOB			Age (Years)		Gender	Relationship to child	Custody
1 (Eldest)								
2								
3								
4								
5 (Youngest)								

Col 60

Coding: Date of birth: Code day, month, year. NA = 99.
Child's age coded in years, NA = 99.
Gender: Female = 1; Male =2; NA = 9.
Relationship to child: Adoptive parent = 1; Step/de facto step parent = 2;
Family relation (eg, aunt/uncle) = 3; Foster parent = 4; Other = 5; NA = 9.
Legal custody: Yes = 1; No = 2; NA = 9.

Record any additional information here: _____

_____

_____

B.6 Are any other people living with you at the moment?

Number ☐

Total number of people in the household?

Total number | | | Col 64

SECTION C. FAMILY FINANCES AND LIVING CONDITIONS

Housing

C.1 What kind of house are you living in at the moment?

Own house	1
Own flat	2
Rented house (private landlord)	3
Rented flat (private landlord)	4
State/council owned house	5
State/council owned flat	6
Single room or bedsit	7
Staying with other family members	8
Other, eg car, caravan, boat. Specify: _____	9

C.2 How long have you lived here? Months | | |

C.3 How many places have you lived in the past 3 years? Number | | | Col 69

Family Finances

C.4 Are you working (in paid employment) at the moment?

(If on maternity leave please note employment details)

Yes	1
No	2

C.5 If yes, specify:

a) Occupation: _____

b) Industry: _____

c) How many hours per week do you work? If no work enter 00. Hours | | | Col 72

d) How much do you receive each week after tax? (If not working enter 0's) Amount | | | | | Col 76 REC03

C.6 Are you in receipt of any of the following Social Welfare benefits?	Yes	No
Domestic Purposes Benefit	1	2
Unemployment Benefit / Community Wage	1	2
Sickness/Invalid's Benefit	1	2
Other Social Welfare Benefit. Specify:	1	2

C.7 How much do you receive in benefit payments per week?

Amount | | | |

C.8 Do you receive any Family Assistance payments (that are not already included above)?

Amount/week | | | |

C.9 Do you receive income from any other source, eg donations from parents, investment income, etc

Amount/week | | | | Col 17

IF NO COHABITING PARTNER ENTER 9's IN C.10 – C.15

C.10 Is your partner working (in paid employment) at the moment?

Yes	1	
No	2	
NA	9	Col 18

C.11 If yes, specify:

a) Occupation: _____

b) Industry: _____

c) How many hours per week does s/he work? Hours | | | Col 18

d) How much does s/he receive each week after tax? (If not working enter 0's)

Amount | | | | | Col 24

C.12 Is your partner in receipt of any of the following Social Welfare benefits?

	Yes	No	NA	
Domestic Purposes Benefit	1	2	9	
Unemployment Benefit / Community Wage	1	2	9	
Sickness/Invalid's Benefit	1	2	9	
Other Social Welfare Benefit. Specify:	1	2	9	Col 28

C.13 How much does your partner receive in benefit payments per week?

Amount | | | | Col 28

C.14 Does your partner receive any Family Assistance payments (that are not already included above)?

Amount/week | | | |

C.15 Does s/he receive income from any other source, eg donations from parents, investment income, etc

Amount/week | | | | Col 37

SECTION D. PREGNANCY

D.1 How many weeks pregnant are you at the moment?

GA		

D.2 Were you trying to get pregnant?

Yes	1
Unsure	2
No	3

Col 40

D.3 What was your reaction when you first heard you were pregnant?

Delighted/very happy	1
Happy	2
Indifferent	3
Upset	4
Very upset	5

D.4 What was your partner's reaction when you told him you were pregnant?

Delighted/very happy	1
Happy	2
Indifferent	3
Upset	4
Very upset	5
No partner	9

Col 4

D.5 When did you first consult a doctor concerning your pregnancy?

Record weeks of pregnancy		

D.6 So far during your pregnancy, have you experienced any of the following problems or illnesses?

a) Vaginal bleeding	0-3 months	Yes	1
		No	2
	4-6 months	Yes	1
		No	2
	7-9 months	Yes	1
		No	2
		NA	9
b) High blood pressure	0-3 months	Yes	1
		No	2
		NA	9
	4-6 months	Yes	1
		No	2
		NA	9
	7-9 months	Yes	1
		No	2
		NA	9

Col 47

Col 50

c) Psychiatric or emotional problems treated by a doctor eg depression Specify: _____	0-3 months	Yes	1	
		No	2	
	4-6 months	Yes	1	
		No	2	
	7-9 months	Yes	1	
		No	2	
		NA	9	Col 53

D.7 Who have you been seeing for antenatal care?

a) Family doctor or GP	Yes	1	
	No	2	
b) Private specialist/Obstetrician	Yes	1	
	No	2	
c) Hospital clinic	Yes	1	
	No	2	
d) Midwife	Yes	1	
	No	2	Col 57

Pregnancy Nutrition

D.8 On average how many servings of the following would you have eaten **per week** during your pregnancy

Number

a) Fruit including fresh, frozen, canned, stewed
(1 serving = 1 apple or 2 small apricots) | | |

Number

b) Vegetables including fresh, frozen, canned
(1 serving = 1 potato, ½ cup cooked vegetables, 1 cup salad greens) | | |

Number

c) Meat including beef, lamb, chicken, fish, shellfish | | |

Number

d) Bread or toast slices (number of slices) | | |

Number

e) Pasta, rice, muesli, cereal
(1 serving = 1 cup cooked rice/pasta/porridge/cornflakes or ½ cup muesli or 2 weetbix) | | |

Number

f) Milk (1 serving = 1 glass) | | |

Number

g) Eggs (1 serving = 1 egg) | | | Col 71

REC 0

SECTION E. DRUG USE DURING PREGNANCY

E.1 Did you smoke cigarettes before or during your pregnancy?

	No. of cigs per day	
Before pregnancy		
1st 3 months		
2nd 3 months		
3rd 3 months		

Col 12

E.2 Did you smoke dope/cannabis before or during your pregnancy?

	No. of joints per week	
Before pregnancy		
1st 3 months		
2nd 3 months		
3rd 3 months		

Col 20

E.3 Did you drink alcohol before or during your pregnancy?

	No. of drinks per week	
Before pregnancy		
1st 3 months		
2nd 3 months		
3rd 3 months		

Col 28

E.4 Did you use benzodiazepines before or during your pregnancy?

	No. of times per week		
Before pregnancy			
1st 3 months			
2nd 3 months			
3rd 3 months			Col 36

E.5 Did you use heroin or other opioids (excluding methadone) before or during your pregnancy?

	No. of times per week		
Before pregnancy			
1st 3 months			
2nd 3 months			
3rd 3 months			Col 44

E.6 Did you use stimulants (eg amphetamines, speed, cocaine) before or during your pregnancy?

Before pregnancy			
1st 3 months			
2nd 3 months			
3rd 3 months			Col 52

SECTION F. MATERNAL WELLBEING
(Edinburgh Postnatal Depression Scale, Cox et al., 1987)

F.1 Right NOW

	Not at all	Somewhat	Moderately	Very much	
I feel calm	1	2	3	4	
I am tense	1	2	3	4	
I feel upset	1	2	3	4	
I am relaxed	1	2	3	4	
I feel confident	1	2	3	4	
I am worried	1	2	3	4	Col 58

F.2 During my PREGNANCY:

	Often	Sometimes	Hardly Ever	Never	
I was able to laugh and see the funny side of things	1	2	3	4	
I looked forward with enjoyment to things	1	2	3	4	
I blamed myself unnecessarily when things went wrong	1	2	3	4	
I felt anxious or worried for no good reason	1	2	3	4	
I felt scared or panicky for no very good reason	1	2	3	4	
Things got on top of me	1	2	3	4	
I was so unhappy that I had difficulty sleeping	1	2	3	4	
I felt sad or miserable	1	2	3	4	
I got so unhappy that I cried	1	2	3	4	
I thought about harming myself	1	2	3	4	Col 68

F.3 In the PAST TWO WEEKS:

	Often	Sometimes	Hardly Ever	Never	
I have been able to laugh and see the funny side of things	1	2	3	4	
I have looked forward with enjoyment to things	1	2	3	4	
I have blamed myself unnecessarily when things went wrong	1	2	3	4	
I have been anxious or worried for no good reason	1	2	3	4	
I have felt scared or panicky for no very good reason	1	2	3	4	
Things have been getting on top of me	1	2	3	4	
I have been so unhappy that I have had difficulty sleeping	1	2	3	4	
I have felt sad or miserable	1	2	3	4	
I have been so unhappy that I have been crying	1	2	3	4	
The thought of harming myself has occurred to me.	1	2	3	4	Col 78

REC 0

SECTION G. DRUG DEPENDENCE
(DSM-IV questions from the Composite International Diagnostic Interview)

Cigarettes

G.1 Over the last 6 months have you smoked a cigarette or cigarettes? If yes, how many cigarettes would you smoke per day?

Non-smoker	1	
<1 per day	2	
1-4 per day	3	
5-9 per day	4	
10-20 per day	5	
21+ per day	6	Col 5

IF RESPONDENT REPORTS SMOKING ASK G.2
OTHERWISE ENDORSE THIS ITEM WITH 9's

G.2	Doesn't Apply	Applies Somewhat	Def. Applies	NA
If you can't get or have a cigarette do you feel tense, irritable, need a cigarette	1	2	3	9
Do you want a cigarette first thing in the morning	1	2	3	9
Do you have headaches or other physical symptoms when you can't get cigarettes	1	2	3	9
Have you more than once wanted to quit or cut down on smoking	1	2	3	9
Have you tried to quit or cut down on your smoking and found you couldn't	1	2	3	9
Can you go a day without having a cigarette	1	2	3	9
Do you think you are dependent on or addicted to cigarettes	1	2	3	9

Have you often had periods of days when you smoked more than you intended	1	2	3	9	Col 13
Have you had to go outside of work or other places so that you could smoke	1	2	3	9	
Have you increased the amount you smoke to get the same effect	1	2	3	9	
Has smoking cigarettes ever caused a problem with your health	1	2	3	9	
Have you ever been advised by a doctor to give up smoking because of your health	1	2	3	9	Col 17

Alcohol

G.3 Over the past month how often would you have drunk alcohol?

Never	1	
Very occasionally (once or twice)	2	
At least weekly	3	
Almost every day	4	Col 18

IF RESPONDENT HAS NEVER DRUNK ALCOHOL IN THE LAST MONTH ENTER 0's IN G.4 – G.5

G.4 On the last occasion you drank how much did you drink?

INTERVIEWER: Find out best 'unit' eg glasses, etc in which to measure drinks and record for that unit. Enter 00 in other boxes

		Number	
Beer	Glasses		
	Handles		
	Jugs		
	Standard bottles		
	Cans/stubbies		
	Flagons		
	Riggers		
Low Alcohol Beer	Glasses		
	Handles		
	Cans/stubbies		
Spirits/Liqueurs	Glasses		
	½ Bottles		
	Bottles		
Mixed Cocktails	Glasses		
Wine	Glasses		
	Bottles		
Wine Cooler	Glasses		
	Bottles		
Fortified Wine	Glasses		
	Bottles		
	Flagons		

Col 30

Other, specify	Glasses			Col 62

G.5 What is the most you have drunk on any one occasion in the past month?

		Number		
Beer	Glasses			
	Handles			
	Jugs			
	Standard bottles			
	Cans/stubbies			
	Flagons			
	Riggers			Col 76

REC 0

Low Alcohol Beer	Glasses		
	Handles		
	Cans/stubbies		
Spirits/Liqueurs	Glasses		
	½ Bottles		
	Bottles		
Mixed Cocktails	Glasses		
Wine	Glasses		
	Bottles		
Wine Cooler	Glasses		
	Bottles		
Fortified Wine	Glasses		
	Bottles		
	Flagons		
Other, specify	Glasses		Col 34

Marijuana

F.1 Have you ever used or tried smoking cannabis (marijuana, grass, dope etc)?

Yes	1	
No	2	Col 35

IF YES TO F.1 ASK F.2 - F.3 OTHERWISE ENDORSE THESE ITEMS WITH 9's AND ASK F.4

F.2 At the present time how often do you use cannabis?

Nearly every day	1	
At least once a week	2	
At least once a month	3	
Less than once a month	4	
Has only used once or twice	5	
Not used cannabis	9	Col 36

F.3 Over the last year has your use of cannabis resulted in any of the following

	Yes	No	NA
You being unable to work or meet other commitments because you were high	1	2	9
Problems with your family	1	2	9
Problems with your friends	1	2	9
Problems with the Police	1	2	9
Problems with your husband/partner/boyfriend	1	2	9
Being in a situation where being high increased your chances of being hurt, having an accident	1	2	9
You having a strong and irresistible desire to smoke cannabis	1	2	9
You wishing to stop or cut down on using cannabis but finding you couldn't	1	2	9
Often using larger amounts of cannabis than you intended to when you started	1	2	9
Using cannabis for longer than you intended to	1	2	9
Spending a great deal of time using cannabis or getting over its effects	1	2	9
Having to use more to get the same effect	1	2	9

Having withdrawal symptoms if you tried to stop or cut down on using cannabis (eg feeling sick, headaches etc)	1	2	9	Col 49
Problems with your health	1	2	9	
Psychological problems	1	2	9	
Have you ever stolen goods or money in order to buy cannabis	1	2	9	Col 52

ASK ALL RESPONDENTS F.4

F.4 Have you ever used or tried any of the following

	Yes	No	
Solvents - glue, petrol, etc	1	2	
Sedatives – downers	1	2	
Stimulants – uppers	1	2	
Heroin/homebake	1	2	
Morphine/MSTs	1	2	
Cocaine	1	2	
LSD, PCP, ecstasy	1	2	
Other prescription medicine to get you high	1	2	
Any other substance. Specify:	1	2	Col 61

IF RESPONDENT HAS USED ANY SUBSTANCE IN F.4
ASK F.5 OTHERWISE ENDORSE THIS ITEM WITH 9

F.5 At the present time (ie over the last month) how often do you use this drug (these drugs)

Nearly every day	1
At least once a week	2
At least once a month	3
Less than once a month	4
Has only used once or twice	5

Not used drugs | 9 | Col 62

SECTION H. PERSONALITY

Read each statement carefully, but don't spend too much time deciding on the answer.

Please answer *every* statement by circling either a T (true) or a F (false) after each question, even if you are not completely sure of the answer.

Remember there are *no* right or wrong answers - just describe your <u>own</u> personal opinions and feelings.

H.1

	True	**False**
I often try new things just for fun and thrills, even if most people think it is a waste of time	1	2
I usually am confident that everything will go well even in situations that worry most people	1	2
I often feel that I am the victim of circumstances	1	2
I can usually accept other people as they are, even when they are very different from me	1	2
I enjoy getting revenge on people who hurt me	1	2
Often I feel that my life has little purpose or meaning	1	2
I like to help find a solution to problems so that everyone comes out ahead	1	2
I could probably accomplish more than I do, but I don't see the point in pushing myself harder than is necessary to get by	1	2
I often feel tense and worried in unfamiliar situations, even when others feel there is little to worry about	1	2
I often do things based on how I feel at the moment without thinking about how they were done in the past	1	2
I usually do things my own way, rather than giving in to the wishes of other people	1	2
I generally don't like people who have different ideas from me	1	2
I would do almost anything legal in order to become rich and famous, even if I would lose the trust of many old friends	1	2

	True	False
I am much more reserved and controlled than most people	1	2
I like to discuss my experiences and feelings openly with friends instead of keeping them to myself	1	2
I have less energy and get tired more quickly than most people	1	2
I seldom feel free to choose what I want to do	1	2
I often consider another person's feelings as much as my own	1	2
I often avoid meeting strangers because I lack confidence with people I do not know	1	2
I like to please other people as much as I can	1	2
I often wish that I was smarter than everyone else	1	2
I am usually so determined that I continue to work long after other people have given up	1	2
I often wait for someone else to provide a solution to my problems	1	2
I often spend money until I run out of cash or get into debt from using too much credit	1	2
Often I have unexpected flashes of insight or understanding while relaxing	1	2
I don't care very much whether other people like me or the way I do things	1	2
I usually try to get just what I want for myself because it is not possible to satisfy everyone anyway	1	2
I have no patience with people who don't accept my views	1	2
I sometimes feel so connected to nature that everything seems to be part of one living organism	1	2
When I have to meet a group of strangers, I am more shy than most people	1	2
I am more sentimental than most people	1	2

Col 77
REC 07

	True	False
I seem to have a sixth sense that sometimes allows me to know what is going to happen	1	2
When someone hurts me in any way, I usually try to get even	1	2
My attitudes are determined largely by influences outside my control	1	2
I often wish I was stronger than everyone else	1	2
I like to think about things for a long time before I make a decision	1	2
I am more hard-working than most people	1	2
I usually stay calm and secure in situations that most people would find physically dangerous	1	2
I do not think it is smart to help weak people who cannot help themselves	1	2
I cannot have any peace of mind if I treat other people unfairly, even if they are unfair to me	1	2
People will usually tell me how they feel	1	2
Sometimes I have felt like I was part of something with no limits or boundaries in time or space	1	2
I sometimes feel a spiritual connection to other people that I cannot explain in words	1	2
I like it when people can do whatever they want without strict rules and regulations	1	2
I would probably stay relaxed and outgoing when meeting a group of strangers, even if I were told they are unfriendly	1	2
Usually I am more worried than most people that something might go wrong in the future	1	2
I usually think about all the facts in detail before I make a decision	1	2
I often wish I had special powers like Superman	1	2
Other people control me too much	1	2

Col 23

	True	False
I like to share what I have learned with other people	1	2
I am usually able to get other people to believe me, even when I know that what I am saying is exaggerated or untrue	1	2
Sometimes I have felt my life was being directed by a spiritual force greater than any human being	1	2
I have a reputation as someone who is very practical and does not act on emotion	1	2
I am strongly moved by sentimental appeals (like when asked to help crippled children)	1	2
I usually push myself harder than most people do because I want to do as well as I possibly can	1	2
I have so many faults that I don't like myself very much	1	2
I have too little time to look for long-term solutions for my problems	1	2
I often cannot deal with problems because I just don't know what to do	1	2
I prefer spending money rather than saving it	1	2
I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone	1	2
If I am embarrassed or humiliated, I get over it very quickly	1	2
It is extremely difficult for me to adjust to changes in my usual way of doing things because I get so tense, tired, or worried	1	2
I usually demand very good practical reasons before I am willing to change my old ways of doing things	1	2
I nearly always stay relaxed and carefree, even when nearly everyone else is fearful	1	2
I find sad songs and movies pretty boring	1	2
Circumstances often force me to do things against my will	1	2
I would rather be kind than get revenge when someone hurts me	1	2

Col 42

	True	False
I often become so fascinated with what I'm doing that I get lost in the moment--like I'm detached from time and place	1	2
I do not think I have a real sense of purpose for my life	1	2
I often feel tense and worried in unfamiliar situations, even when others feel there is no danger at all	1	2
I often follow my instincts, hunches, or intuition without thinking through all the details	1	2
Other people often think that I am too independent because I won't do what they want	1	2
I often feel a strong spiritual or emotional connection with all the people around me	1	2
I usually try to imagine myself in other people's shoes, so I can really understand them	1	2
Principles like fairness and honesty have little role in some aspects of my life	1	2
I am better at saving money than most people	1	2
Even when most people feel it is not important, I often insist on things being done in a strict and orderly way	1	2
I feel very confident and sure of myself in almost all social situations	1	2
My friends find it hard to know my feelings because I seldom tell them about my private thoughts	1	2
I like to imagine my enemies suffering	1	2
I am more energetic and tire less quickly than most people	1	2
I often stop what I am doing because I get worried, even when my friends tell me everything will go well	1	2
I often wish I was more powerful than everyone else	1	2
Members of a team rarely get their fair share	1	2
I don't go out of my way to please other people	1	2

Col 61
REC08

	True	False
I am not shy with strangers at all	1	2
I spend most of my time doing things that seem necessary but not really important to me	1	2
I don't think that religious or ethical principles about what is right and wrong should have much influence in business decisions	1	2
I often try to put aside my own judgments so that I can better understand what other people are experiencing	1	2
Many of my habits make it hard for me to accomplish worthwhile goals	1	2
I have made real personal sacrifices in order to make the world a better place--like trying to prevent war, poverty and injustice	1	2
I prefer to wait for someone else to take the lead in getting things done	1	2
I usually respect the opinions of others	1	2
My behaviour is strongly guided by certain goals that I have set for my life	1	2
It is usually foolish to promote the success of other people	1	2
I usually like to stay cool and detached from other people	1	2
I am more likely to cry at a sad movie than most people	1	2
I recover more quickly than most people from minor illnesses or stress	1	2
I often break rules and regulations when I think I can get away with it	1	2
I need much more practice in developing good habits before I will be able to trust myself in many tempting situations	1	2
I wish other people didn't talk as much as they do	1	2
Everyone should be treated with dignity and respect, even if they seem to be unimportant or bad	1	2
I like to make quick decisions so I can get on with what has to be done	1	2

Col 23

	True	False
I am usually confident that I can easily do things that most people would consider dangerous (such as driving an automobile fast on a wet or icy road)	1	2
I like to explore new ways to do things	1	2
I enjoy saving money more than spending it on entertainment or thrills	1	2
I have had personal experiences in which I felt in contact with a divine and wonderful spiritual power	1	2
I have had moments of great joy in which I suddenly had a clear, deep feeling of oneness with all that exists	1	2
Most people seem more resourceful than I am	1	2
I often feel like I am a part of the spiritual force on which all life depends	1	2
Even when I am with friends, I prefer not to open up very much	1	2
I think my natural responses now are usually consistent with my principles and long-term goals	1	2
I believe that all life depends on some spiritual order or power that cannot be completely explained	1	2
Often when I look at an ordinary thing, something wonderful happens--I get the feeling that I am seeing it fresh for the first time	1	2
I usually feel tense and worried when I have to do something new and unfamiliar	1	2
I often push myself to the point of exhaustion or try to do more than I really can	1	2
My will power is too weak to overcome very strong temptations, even if I know I will suffer as a consequence	1	2
I hate to see anyone suffer	1	2
If I am feeling upset, I usually feel better around friends than when left alone	1	2
I wish I were better looking than everyone else	1	2
I love the blooming of flowers in the spring as much as seeing an old friend again	1	2

Col 42

	True	False
I usually look at a difficult situation as a challenge or opportunity	1	2
People involved with me have to learn how to do things my way	1	2
I usually feel much more confident and energetic than most people, even after minor illnesses or stress	1	2
When nothing new is happening, I usually start looking for something that is thrilling or exciting	1	2

Col 57
REC09

Control Family Extra Information.

1. Have you or your child's biological father ever suffered from any of the following illnesses? Code 9 if not known

   Note: For mother, code only if illness occurred prior to this pregnancy

Mother

	Yes	No
Epilepsy	1	2
Diabetes	1	2
Depression	1	2
High blood pressure	1	2
Thyroid trouble	1	2
Anaemia	1	2
Psychiatric or mental illness	1	2

Col 11

2. Father

	Yes	No	NA
Epilepsy	1	2	9
Diabetes	1	2	9
Depression	1	2	9
High blood pressure	1	2	9
Thyroid trouble	1	2	9
Anaemia	1	2	9
Psychiatric or mental illness	1	2	9

Col 18

LIFE EVENTS

3. In the last year, have any of the following events occurred to you?

INTERVIEWER: IF "YES" ASK "HOW UPSET OR DISTRESSED WERE YOU BY THIS?"

	Very Upset	Upset	Mildly Upset	Not Upset	No Event
Moved house	5	4	3	2	9
Took out a mortgage	5	4	3	2	9
Built a home or had one built	5	4	3	2	9
Remodelled a home	5	4	3	2	9
Increased financial problems from taking on a mortgage or purchasing a business	5	4	3	2	9
Partner became unemployed	5	4	3	2	9
Partner changed his job	5	4	3	2	9
Partner took a cut in wage or salary without a demotion	5	4	3	2	9
Respondent started a new job	5	4	3	2	9
Respondent took a cut in wage or salary without a demotion	5	4	3	2	9
Someone stayed on in the household after he/she was expected to leave	5	4	3	2	9
Serious family argument other than with spouse	5	4	3	2	9
Family member other than partner or child died	5	4	3	2	9
Close friend died	5	4	3	2	9
Had serious or prolonged disagreements with parents/in-laws	5	4	3	2	9
Serious financial problems	5	4	3	2	9

Suffered a financial loss or loss of property not related to work	5	4	3	2	9	Col
Foreclosure of mortgage or loan	5	4	3	2	9	
Became engaged	5	4	3	2	9	
Married	5	4	3	2	9	
Relations with partner changed for the worse without separation or divorce	5	4	3	2	9	
Serious or prolonged arguments with partner/ex-partner if separated within year	5	4	3	2	9	
Divorce	5	4	3	2	9	
Separation from partner	5	4	3	2	9	
Reconciliation with partner (after divorce or legal separation)	5	4	3	2	9	
Robbed	5	4	3	2	9	
Legal problems	5	4	3	2	9	
Partner involved in court case	5	4	3	2	9	
Injury (respondent)	5	4	3	2	9	
Unable to get treatment for an illness or injury (respondent)	5	4	3	2	9	
Serious illness or accident of partner	5	4	3	2	9	
Serious illness or accident (study child)	5	4	3	2	9	
Serious illness or accident of child (other than survey child)	5	4	3	2	9	
Serious illness (other family members)	5	4	3	2	9	
Miscarriage or still-birth	5	4	3	2	9	
Pet died	5	4	3	2	9	Col

F.2 In the last year, have any other events occurred which have upset you or caused you distress? Describe up to **three** such incidents and degree of distress caused.

Event 1: _____	Very upset	5
_____	Upset	4
_____	Mildly upset	3
_____	No event	1
Event 2: _____	Very upset	5
_____	Upset	4
_____	Mildly upset	3
_____	No event	1
Event 3: _____	Very upset	5
_____	Upset	4
_____	Mildly upset	3
_____	No event	1

Col 5

REC

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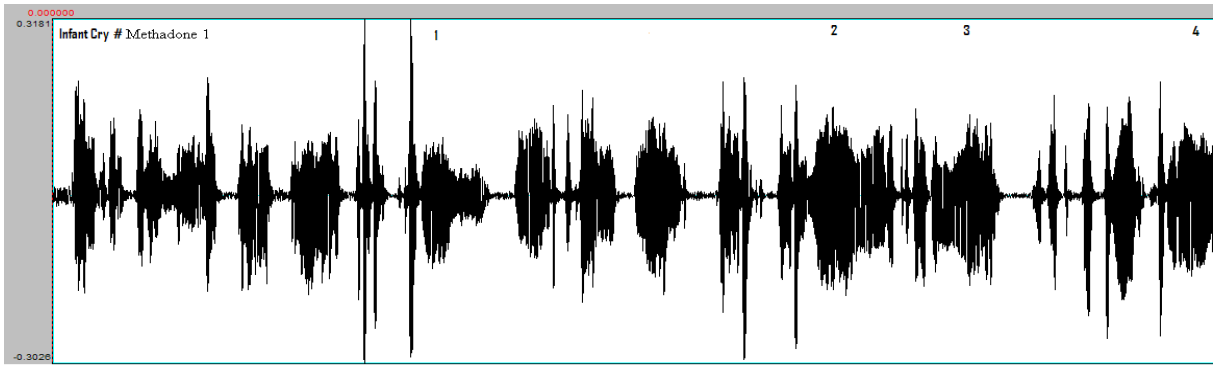
Appendix 5: Neonatal Abstinence Scoring Sheet Used in the Current Study

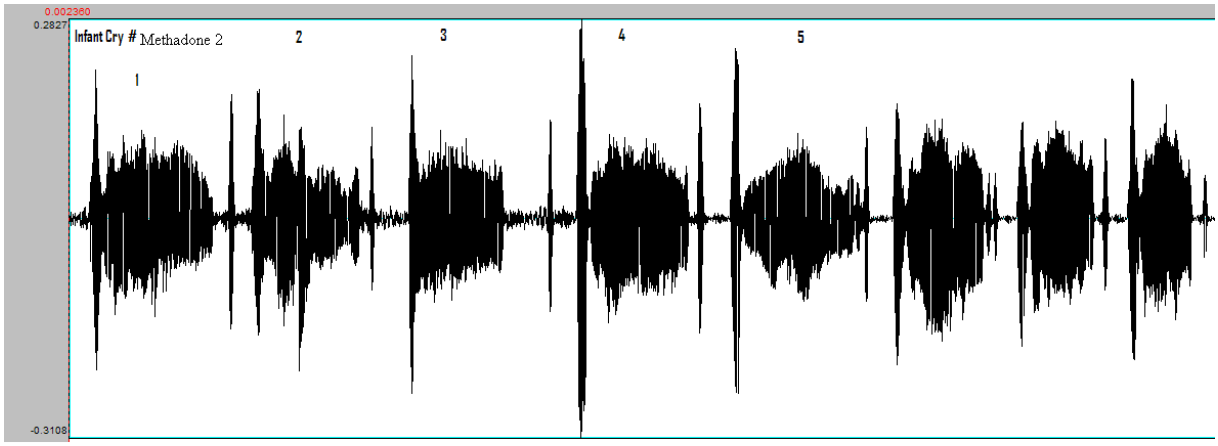
NEONATAL ABSTINENCE SCORE*
Date_____

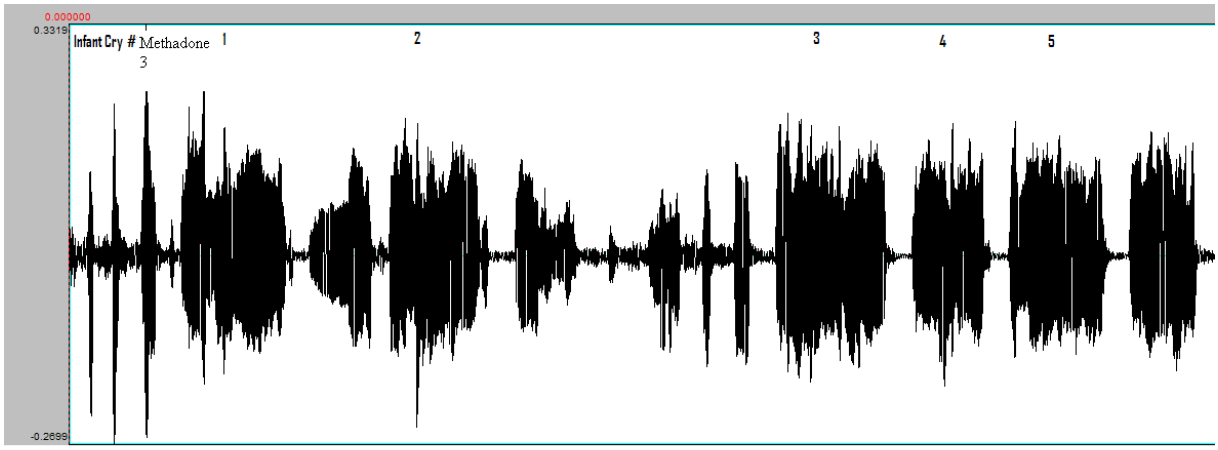
SYSTEM	SIGNS AND SYMPTOMS	SCORE	24	2	4	6	8	10	12	14	16
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES	High-pitched Cry Continuous High-pitched Cry	2 3									
	Sleeps <1hr After Feeding Sleeps <2hrs After Feeding Sleeps <3hrs After Feeding	3 2 1									
	Hyperactive Moro Reflex Markedly Hyperactive Moro Reflex	2 3									
	Mild Tremors Disturbed Moderate-severe Tremors Disturbed	1 2									
	Increased Muscle Tone	2									
	Excoriation (Specific Area)	1									
	Myoclonic Jerks	3									
	Generalized Convulsions	3									
CENTRAL NERVOUS SYSTEM DISTURBANCES	Sweating	1									
	Fever <37.2-38.2EC Fever >38.4EC	1 2									
	Frequent Yawning (>3-4 Times)	1									
	Mottling	1									
	Nasal Stuffiness	1									
	Sneezing (>3-4 Times)	1									
	Nasal Flaring	2									
	Respiratory Rate >60/min Respiratory Rate >60/min with Retractions	1 2									
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1									
	Poor Feeding	2									
	Regurgitation Projectile Vomiting	2 3									
	Loose Stools Watery Stools	2 3									
SUMMARY	TOTAL SCORE										
	SCORER'S INITIALS										
	Initiation of Therapy (+) Increase in Therapy (↑) Decrease in Therapy (↓) Discontinue Therapy (!)										

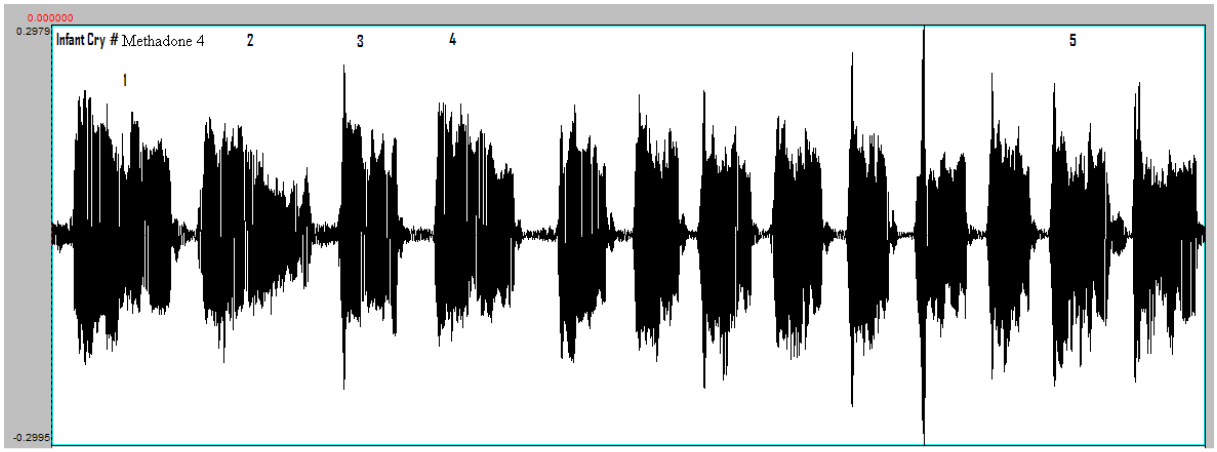
*Based on Finnegan Scoring System

Appendix 6: Cry *wav* Forms of the 20 Infants Analysed






0.000000
0.3319
Infant Cry # Methadone 3
1
2
3
4
5
-0.2699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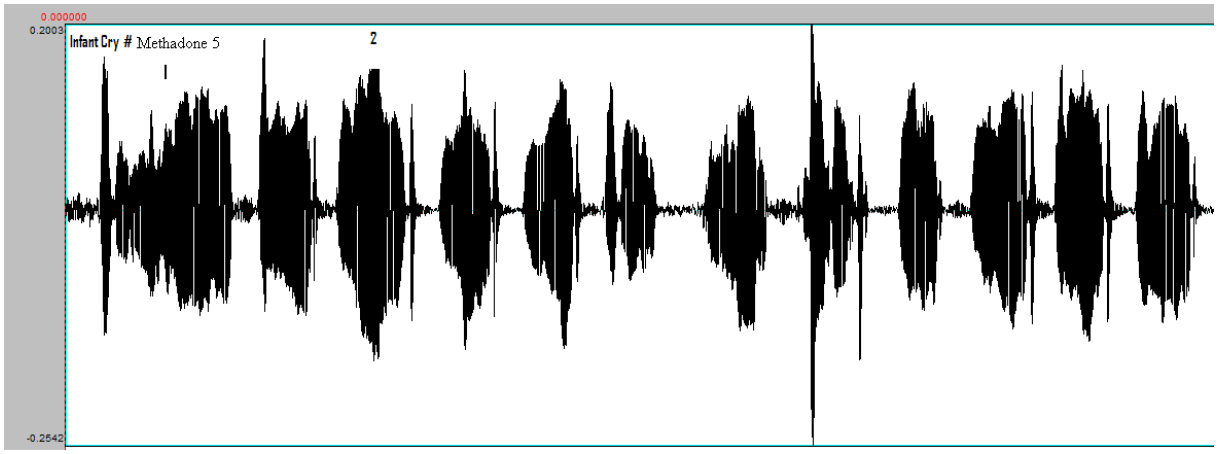
Infant Cry # Methadone 4
1
2
3
4
5
-0.2995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Infant Cry # Methadone 5
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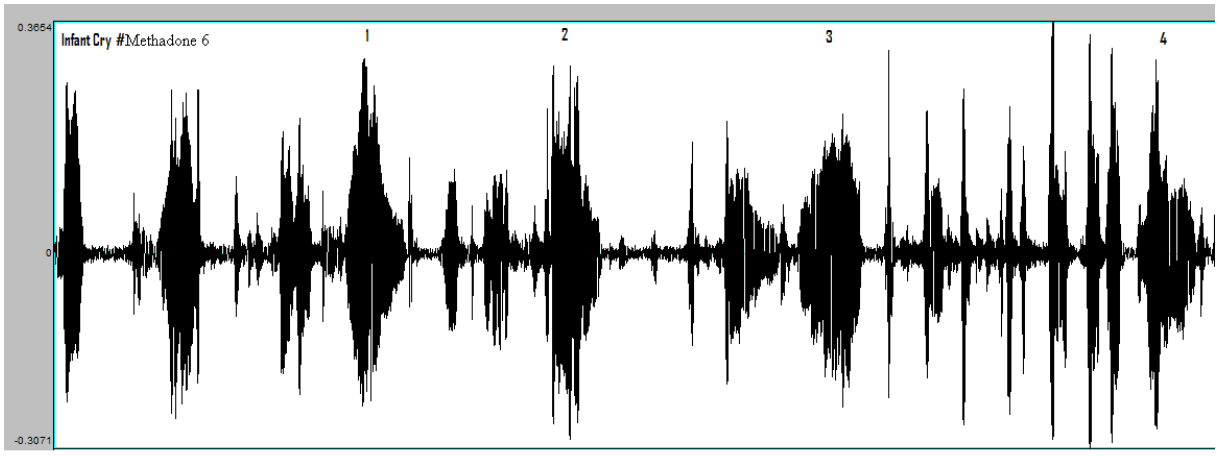
2
-0.2542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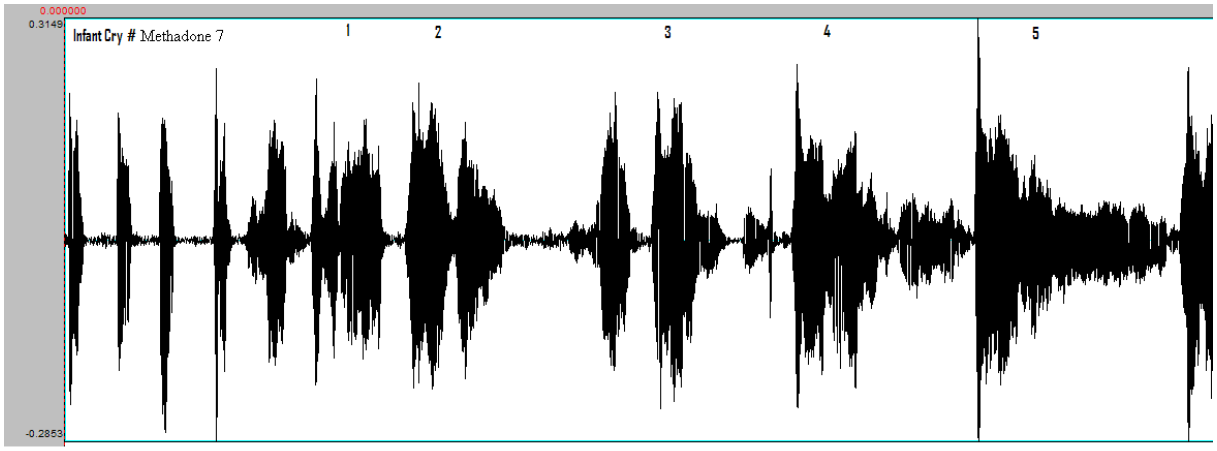
Infant Cry #Methadone 6
1
2
3
4
0
-0.3071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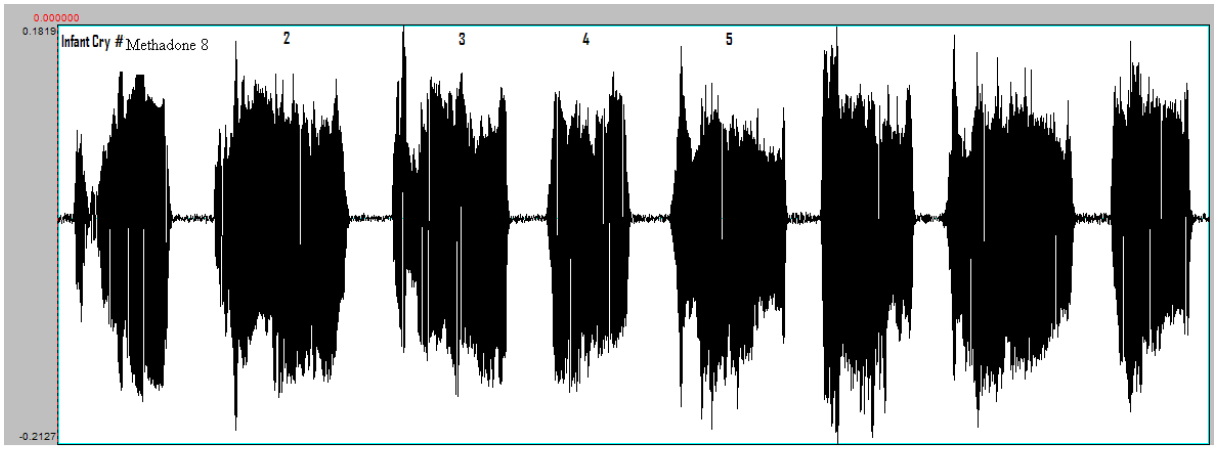
0.3149
Infant Cry # Methadone 7
1
2
3
4
5
-0.2853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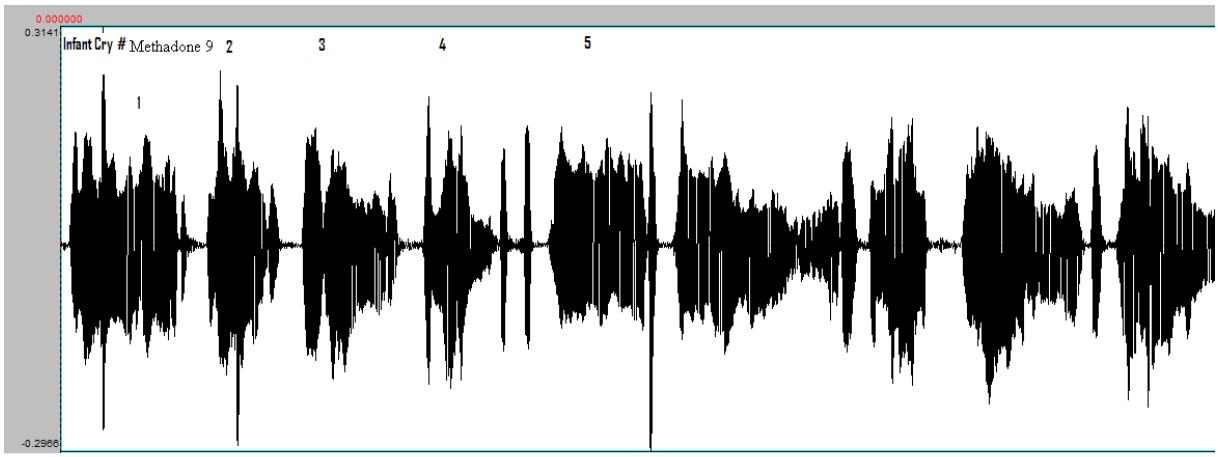
Infant Cry # Methadone 8
2
3
4
5
-0.2127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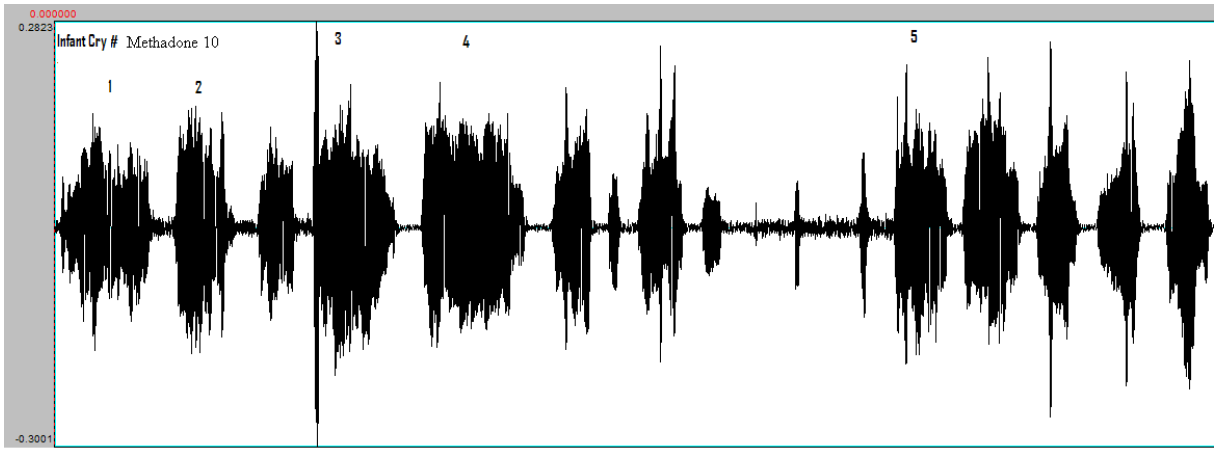
Infant Cry # Methadone 9
1
2
3
4
5
-0.2966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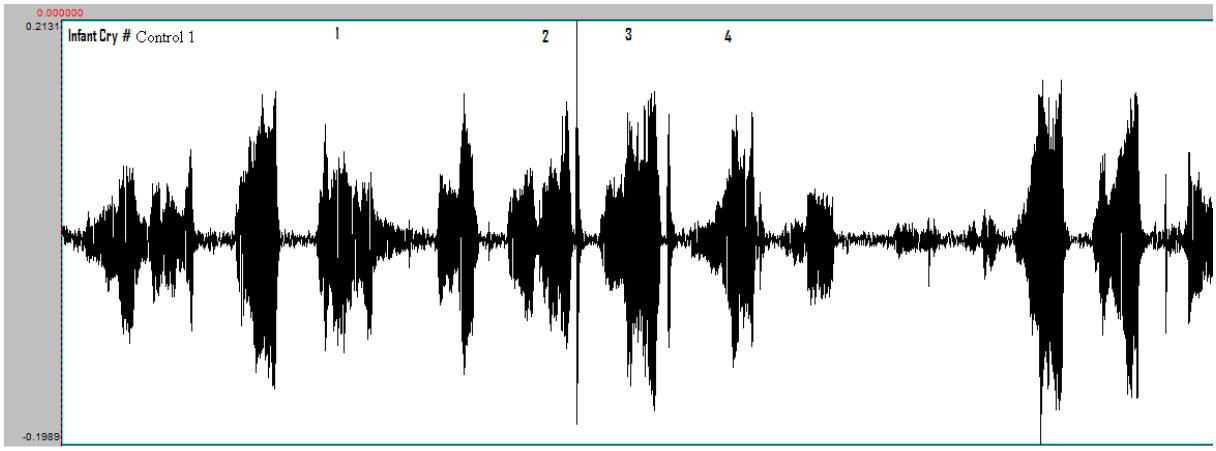
Infant Cry # Methadone 10
1
2
3
4
5
-0.3001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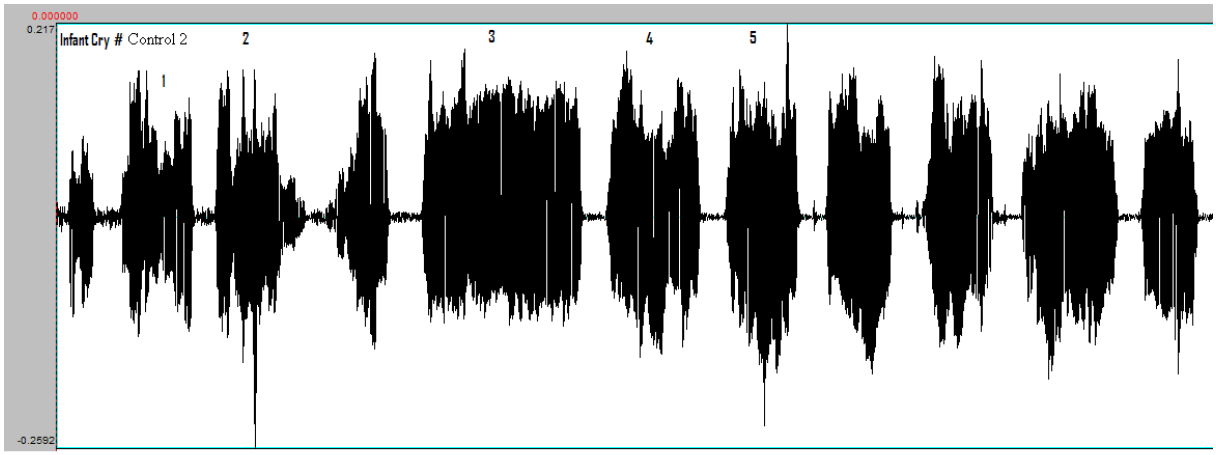
Infant Cry # Control 1
1
2
3
4
-0.1989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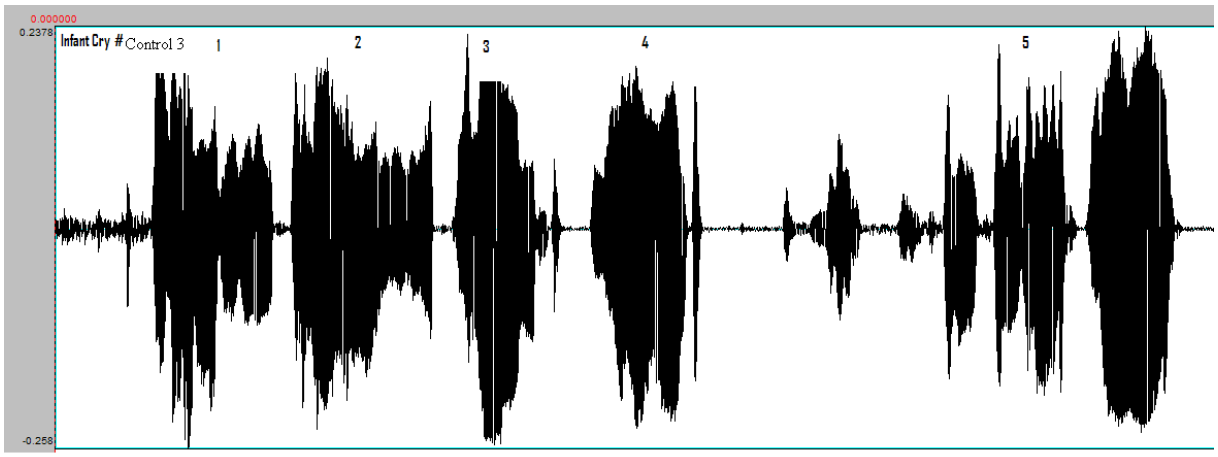
Infant Cry # Control 2
1
2
3
4
5
-0.2592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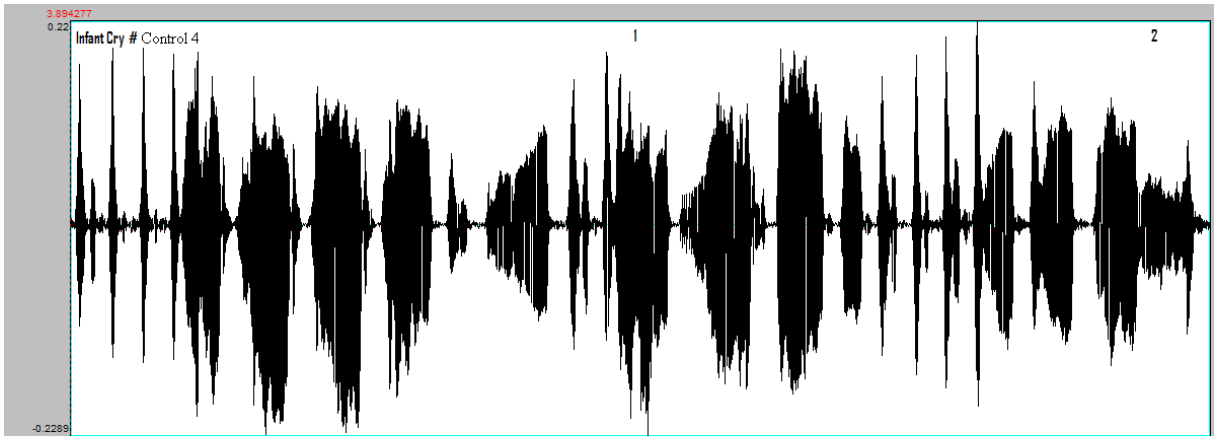
Infant Cry # Control 3
1
2
3
4
5
-0.258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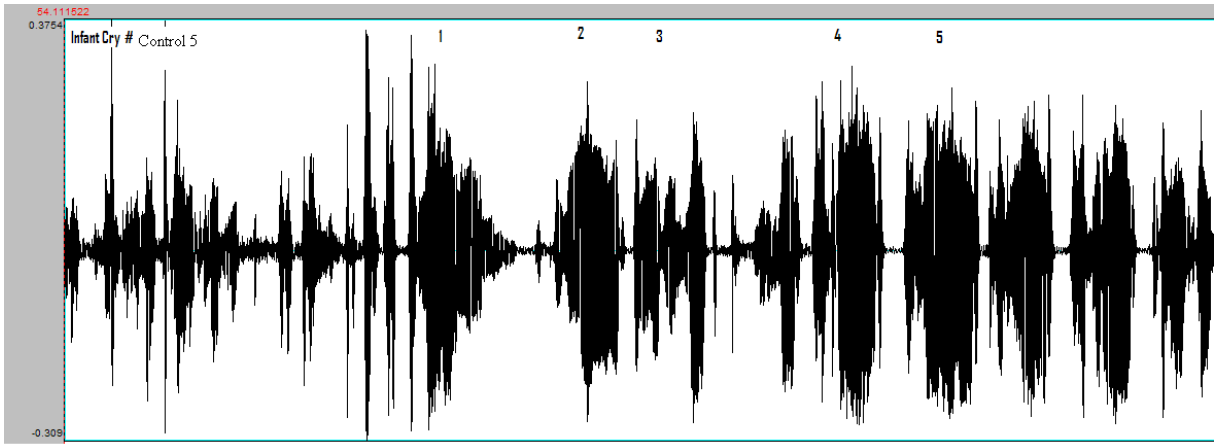
Infant Cry # Control 4
1
2
-0.2289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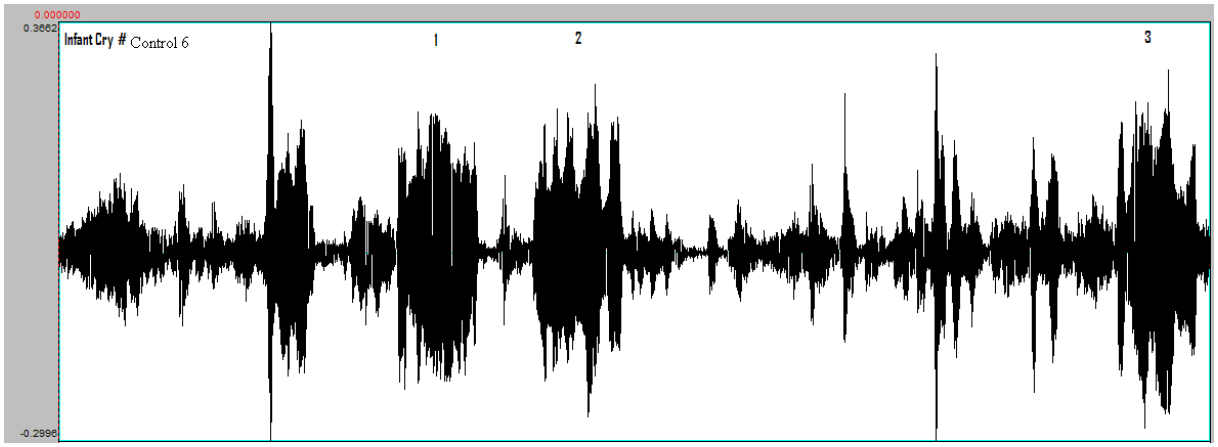
Infant Cry # Control 5
1
2
3
4
5
-0.309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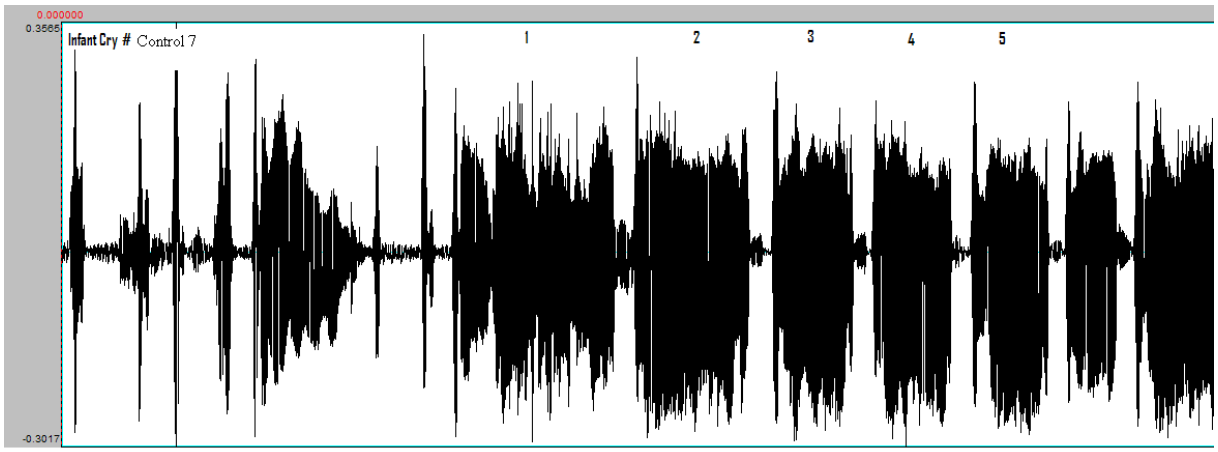
Infant Cry # Control 6
1
2
3
-0.2996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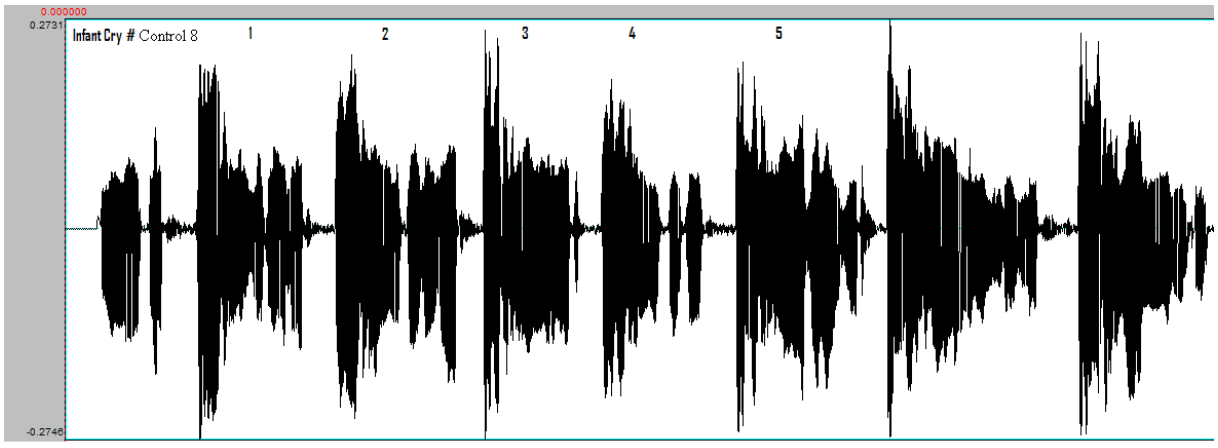
Infant Cry # Control 7
1
2
3
4
5
-0.3017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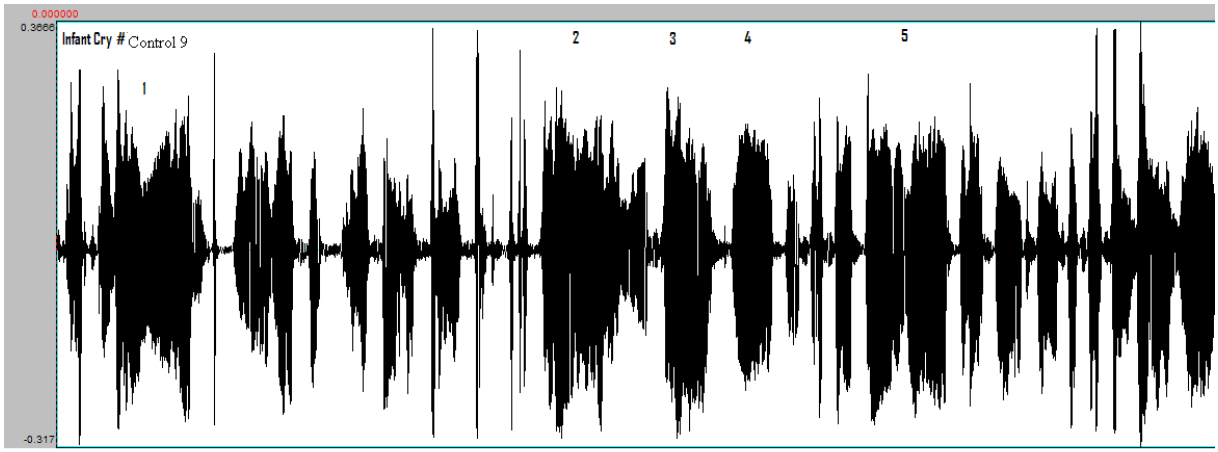
Infant Cry # Control 8
1
2
3
4
5
-0.2746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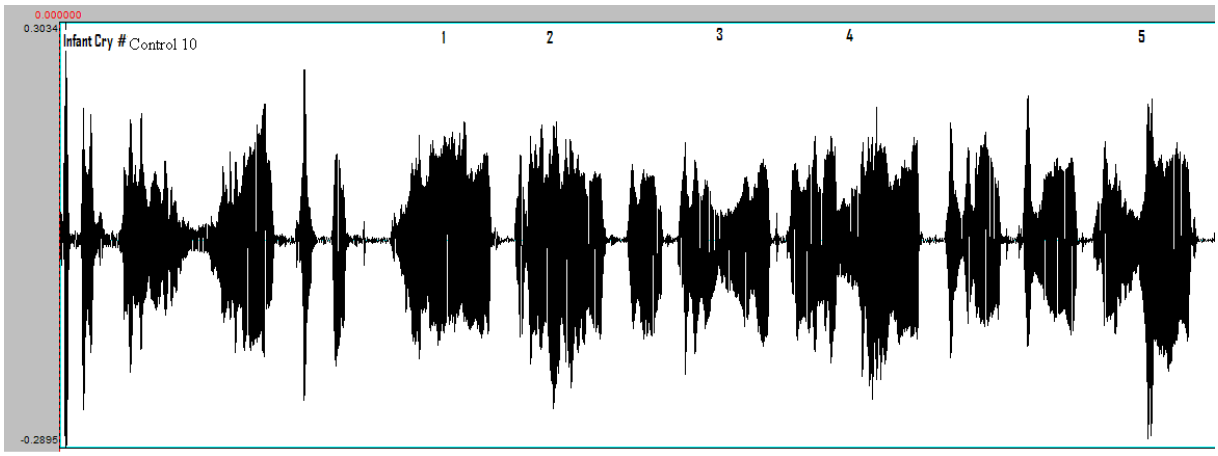
0.3666
Infant Cry # Control 9
1
2
3
4
5
-0.317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0.3034
Infant Cry # Control 10
1
2
3
4
5
-0.2895